STUDIES IN STERIC HINDRANCE WITH SPECIAL REFERENCE TO THE AROMATIC IODO-CHLORIDES.

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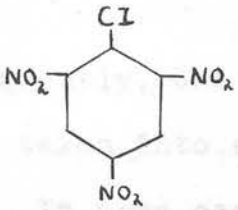
G E N E R A L I N T R O D U C T I O N.

The presence of functional groups in a chemical organic compound confers upon that compound a specific character, and many properties of the molecule are due to the presence of such groups. In a chemical reaction, only these functional groups are supposed to react, the rest of the molecule remaining unaltered; for example, in the reduction of nitrobenzene to aniline the only change is the conversion of the nitro group into an amino group.

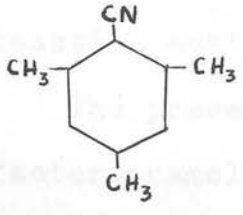
This, however, is only qualitatively true. The reactivity of a functional group is dependent upon the nature of the rest of the molecule, and is specially influenced by other substituents in the molecule. Those substituents situated closely in space - for example, ortho-substituents in aromatic organic compounds - in many cases effect a diminution or inhibition of reactivity. This retardation or inhibition of reactivity by neighbouring groups is known as "Steric Hindrance". The generally accepted explanation of this phenomenon is that the neighbouring atoms or groups, by their "size" or arrangement in space, reduce the number of effective collisions between the molecules of the reagent and the reacting group of the molecule concerned. The term "Steric

Hindrance" has received increased attention within recent years as a result of the theory of restricted rotation about a single bond. This aspect of the problem has been studied intensively in the diphenyl series.

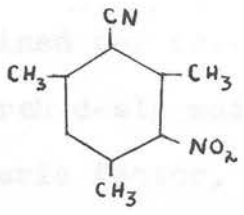
It is now clearly recognised that in many cases factors, other than steric factors, have to be considered. For instance, the introduction of substituents into a molecule may result, not in a diminution of reactivity, but in an increase. This increase in reactivity may even be caused by substituents in the ortho position. To take one example: The chlorine atom in picryl chloride



is very reactive, a fact first recognised by Pisani in 1854. Further, Küster and Stallberg (Ann., 1894, 278, 207) showed that whereas the hydrolysis of 2:4:6-trimethyl benzonitrile (A) is completely hindered under certain conditions by the two ortho methyl groups, the hydrolysis of 2:4:6-trimethyl-3-nitro benzonitrile (B) is comparatively easily effected.

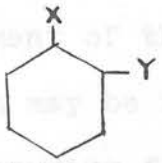


(A.)



(B.)

The effect of a functional group, Y, on the reactivity of another functional group, X, must therefore depend on two factors:-



(a) Bulk of Y - If X and Y are closely situated, as for example when they are situated ortho to one another, this factor will be important and will result most frequently in decreased reactivity.

(b) Chemical or electronic nature of Y - This effect is displayed by groups in all positions in the molecule and may, or may not, give rise to an increase in reactivity.

Consequently, the interplay of these two factors must be taken into account in a consideration of reactivity. In some cases both factors may exert an influence; in others, one or the other may predominate, but unfortunately at present it is not possible to separate the two factors. This will only be possible when the exact mechanism of each reaction is known with certainty and the electronic theories, as applied to organic chemistry, are co-ordinated into a complete whole. At present it is difficult to make generalisations and it seems that every reaction must be examined per se.

The present research deals mainly with the first factor, namely the steric factor, the existence

of which is obvious to all engaged in preparative organic chemistry.

An attempt has been made here to give briefly the development of the idea of steric hindrance; the objections which may be raised against it; and the necessity for assuming factors other than steric in influencing the reactivity of organic compounds.

The importance of the "size" of a substituent was first stressed by Kehrmann (Ber., 1888, 21, 3315) and later by Victor Meyer (Ber., 1894, 27, 510). Objections to this hypothesis, however, have been raised by Michael (Ber., 1909, 42, 310) and Rosanoff and Praeger (J.A.C.S., 1908, 30, 1895), based upon the results obtained in the direct esterification of aromatic carboxylic acids. These authors merely heated the alcohol and aromatic acid together at high temperatures with no catalyst, as compared with Meyer who used hydrochloric acid as a catalyst. They found, it is true, that the ortho derivatives had the smallest velocity of esterification, but they also found that halogen and nitro groups had only a small effect in contrast to methyl groups where the velocity was greatly reduced. They, therefore, questioned the spatial hypothesis, since halogen or nitro groups, because of their greater "size" or volume, should exert a stronger hindering influence than the smaller methyl group. Other authors, however, point out (see Goldschmidt, "Stereochemie", 1933, p. 468) that

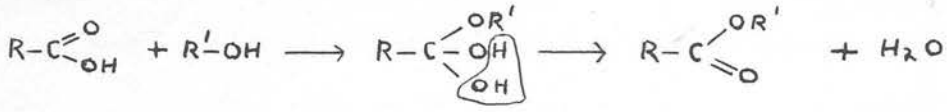
in the direct esterification in the absence of mineral acids the autocatalytic effect of the aromatic acids themselves is not to be neglected. Due to the greater acidity of the halogen or nitro benzoic acids, the esterification is accelerated and the hindering effect of the ortho substituents is partly neutralised. Thus in these strong acids, as a total effect, less hindrance is observed than in the weak toluic acids where the steric factor apparently predominates. Other cases of abnormal reaction velocity due to ortho substitution will be referred to later, showing that collective factors have to be considered.

The typical cases of steric hindrance involve a considerable lowering of reaction velocity, though not a complete inhibition of the reaction. In many cases, more energetic reaction conditions overcome this retardation. Thus 2:4:6-trichloro benzoic acid cannot be esterified under the usual conditions with alcoholic hydrochloric acid even at boiling point, but can be esterified without catalyst at higher temperatures (Rosanoff and Praeger, loc. cit.). Further, it appears that in one and the same compound hindrance may be observed with one reagent and not with another. For example, powerful hindrance is found in the esterification of diortho-substituted aromatic carboxylic acids with alcoholic hydrochloric or sulphuric acid (Wegscheider, Ber., 1895, 28, 3127), but not in the esterification with diazomethane

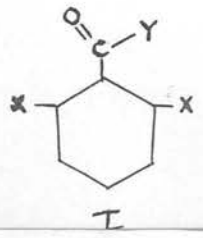
(Pechmann, Ber., 1898, 31, 501)

$$R \cdot COOH + CH_2N_2 \longrightarrow R \cdot COOCH_3 + N_2$$

Lock (Oestr. chem. Zeit., 1934, 19, 3) observes that in the great majority of cases where steric hindrance due to ortho-substituents is observed, the formation of an intermediate addition-compound can be assumed, such as Wegscheider (Ber., 1895, 28, 1468) and Angeli (Ber., 1896, 29, 591) assume in the formation of esters from carboxylic acids according to the Henry scheme (Ber., 1877, 10, 2041).



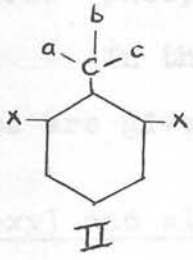
The suggestion has consequently been put forward that the ortho-substituents in the first place prevent the formation of this addition-compound, but the question must remain open, as the mechanism of many reactions, particularly that of esterification, still remains to be elucidated. In agreement, however, with this hypothesis is the fact that mesitylene carboxylic acid ester only slowly adds on sodium alcoholate (Pechmann, loc. cit.). Addition compound formation can be assumed in C = C compounds, as in the addition of halogen or halogen acids to cinnamic acid, in C ≡ N compounds, and especially in compounds of the type (I)



I

y = OH (acids); OR (esters)
Cl (acid chlorides); NH_2 (amides)
CH_3 (acetophenones); C_6H_5 (benzophenones).

In all these cases steric hindrance is observed, but instances of it when Y = H, i.e. in aldehydes, are very rare and at the most problematic. It may be that the small space occupied by the hydrogen atom does not hinder the addition formation, whilst the larger groups, e.g. methyl groups in acetophenones, do so. On the other hand, compounds of the toluene type (II), whose reactions do not necessitate addition formation, do not display steric effects.



II

a,b,c = 3H (toluenes)

a,b,c = 3Cl (benzotrichlorides)

a,b = 2H
c = Cl (benzyl chlorides)

a,b = 2Cl
c = H (benzal chlorides)

Therefore it would seem that steric hindrance is to be observed only in reactions involving an addition mechanism, i.e. in compounds with unsaturated groups. As already mentioned, the esterification of aromatic acids is hindered in the alcohol-hydrochloric acid method, but not when diazomethane is used. This may be due to the fact that the former reaction proceeds according to an addition scheme, whilst the latter does not.

Support to the hypothesis of intermediate addition-compound formation is given by the frequency with which steric hindrance is observed in compounds containing a tertiary nitrogen atom. Here, of course, the addition of other molecules, as in the formation

of quaternary ammonium salts from tertiary bases, takes place by a change of valency of the nitrogen atom, an addition compound being formed.

Another factor in steric hindrance in diortho-substituted groups is the "size" of the reagent used. Anschutz and Delijski (Ann., 1932, 493, 241) showed that certain diortho-substituted phenolic hydroxyl groups do not react with phosphorus pentachloride, but do so with the less reactive but "smaller" phosphorus trichloride.

In the following, the reactions of various groups are given under their appropriate headings.

Carboxyl and allied groups: acids, esters, amides and acid chlorides.

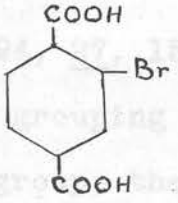
Victor Meyer's researches on the esterification of aromatic carboxylic acids with alcohol and hydrochloric acid led to the enunciation of his Esterification Law - that diortho-substituted benzoic acids are only esterified in small amount or not at all (Ber., 1894, 27, 510). With different co-workers he found that the fluorine atom, methyl and hydroxyl groups only have a small effect, especially on heating, whilst the heavier halogens and the nitro group practically prevent esterification, even at the boiling point. He tried to correlate the steric effect of atoms or groups with their atomic or radical weight, postulating that the greater the weight the greater

the effect. But if this were true, the list of substituents in order of increasing weight, and thus in order of their effect, should be

$H\ (1) < CH_3\ (15) < OH\ (17) < F\ (19) < Cl\ (35{\cdot}5)$
$< NO_2\ (46) < Br\ (80) < I\ (127)$

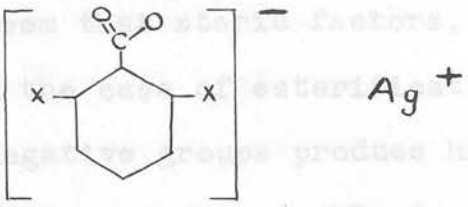
But quantitative measurements with Kellas (Zeit. phys. Chem., 1897, 24, 221) on the esterification of various mono-substituted benzoic acids showed that, whilst substituents in the ortho position all showed a steric effect, that of the nitro group was greater than both iodine and bromine, and that of methyl greater than chlorine; i.e., $NO_2 > I > Br > CH_3 > Cl$. It is obvious that there is no correlation therefore. Also para-substituents invariably exerted a greater effect than meta-substituents, showing that the reaction is susceptible to factors other than steric influences.

In mono-substituted dicarboxylic acids of the type

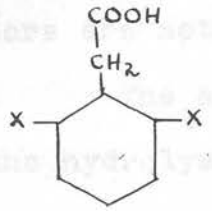


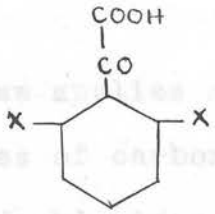
the -COOH farther from the substituent is always first esterified (Wegscheider, Mon., 1900, 21, 638). This behaviour was also observed in the formation of oximes of quinones by Kehrmann. Investigation of ortho-substituted phthalic acids showed that the -COOH group has a steric effect comparable to that of $-CH_3$ or -OH (Sudborough and Meyer, 1894, 27, 3148 ; Wegscheider and Lipschitz, Mon., 1900, 21, 787).

The esters of diortho-substituted carboxylic acids can be easily obtained from their silver salts with methyl iodide. Wegscheider (Ber., 1895, 28, 1468) explains this by saying that this reaction will be independent of ortho-substituents because the silver ion is removed from their influence.



Perhaps the chief argument in favour of Meyer's spatial ideas is the unhindered esterification of acids of the type

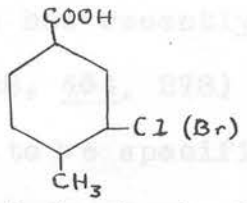




In such cases the esterification is unhindered and Meyer argued (Ber., 1894, 27, 1587 ; 1895, 28, 3198) that, by interposing a grouping between the benzene nucleus and the -COOH group, the -COOH had been removed from the influence of substituents. His argument is not conclusive, however, as phenyl acetic acid itself is esterified with greater ease than benzoic acid.

Numerous anomalies have been brought to light in esterification which cannot be explained on a steric principle. To mention only one, Auwers

and Harres (Zeit. phys. Chem., (A) 1929, 143, 17) obtained remarkably low velocity of esterification with 3-chloro and 3-bromo-4-methyl benzoic acid.



But it would seem that steric factors, on the whole, predominate in the case of esterification, since both positive and negative groups produce hindrance. Also fluorine, a smaller atom than chlorine or bromine, but much more powerfully electronegative, only exerts a small effect. The behaviour of the nitro group, compared to the halogens, shows, however, that other factors are not absent.

The esterification law applies qualitatively to the hydrolysis of derivatives of carboxylic acids, such as esters, amides and acid chlorides. In general, it is found that diortho-substituted derivatives are the most difficult to hydrolyse; yet it is not always easy to correlate their behaviour with the esterification of the corresponding acid.

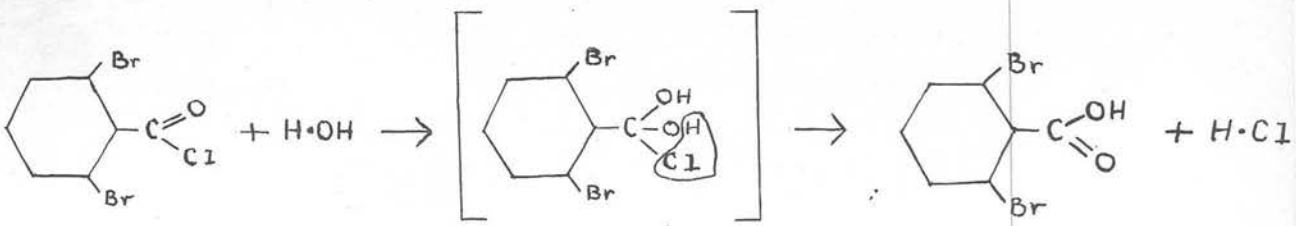
Kellas studied the hydrolysis of the methyl esters of various benzoic acids (Zeit. phys. Chem., 1897, 24, 251) and found that the results obtained differed appreciably from those expected from the esterification law. One ortho methyl group has a stronger hindering effect than bromine or iodine similarly placed, but whereas the three former exhibit

hindrance, chlorine, and particularly the nitro group, show a strong accelerating effect. Meta and para substituted acids likewise show abnormal velocity of hydrolysis. This has recently been verified by Kindler (Ann., 1928, 464, 278) who contends that other effects have also to be specified.

From a study of mono- and diortho-substituted bromo-benzoyl chlorides Sudborough (J.C.S., 1895, 67, 601) concluded that the resistance to decomposition with dilute alkali was in the order:

di-ortho > mono-ortho > unsubstituted.

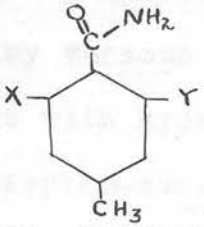
The hydrolysis was studied quantitatively by Olivier (Rec. trav. Chim., 1929, 48, 227). Using aqueous acetone as hydrolysing agent he found that the velocity of hydrolysis of 2:6-dibromo-benzoyl chloride was only one-hundredth of that of the unsubstituted compound. Therein he sees a clear instance of steric hindrance in the Meyer sense, due to the hindering of the formation of the addition compound according to the scheme:



But Olivier's results also show that o-nitro-, chloro-, and bromo-benzoyl chlorides have a greater velocity of hydrolysis than benzoyl chloride itself, increasing in the order given, whilst that of o-methyl benzoyl

chloride is very great. This affords additional proof that steric factors may be counter-balanced by others.

Steric effects in the hydrolysis of acid amides have been observed by various workers. Jacobson (Ber., 1889, 22, 1219) pointed out the extreme stability of pentamethylbenzamide, whilst Claus (Ann., 1891, 265, 364; 266, 223; 1892, 269, 203) found various diortho-substituted derivatives of p-toluylamide to be unusually stable to hydrolysis.

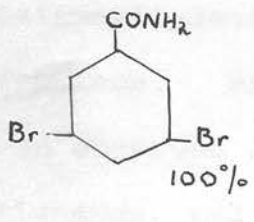


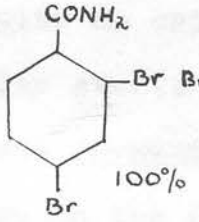
x = y = NO_2

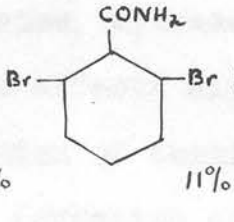
x = y = Br

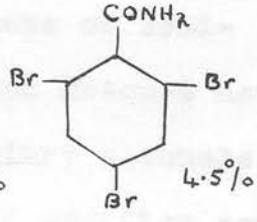
x = NO_2 ; y = Br

Sudborough, Jackson and Lloyd (J.C.S., 1895, 67, 601; 1897, 71, 229) obtained the following results for the quantities of acid formed in a given time from the compounds noted, using sulphuric acid as hydrolysing agent.



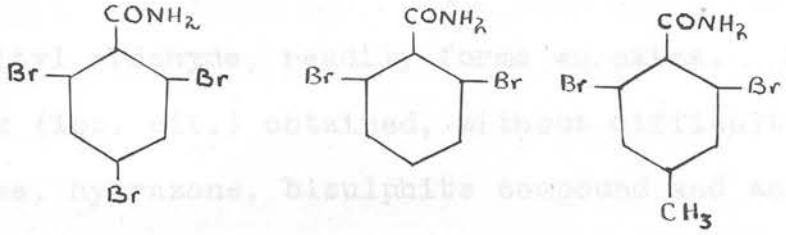






Remsen and Reid (Am. Chem. Jour., 1899, 21, 340), studying mono-substituted acid amides, showed the definite retarding effect of ortho groups. More recently, however, Buning (Rec. trav. Chim., 1921, 40, 327) has shown that the following acid amides

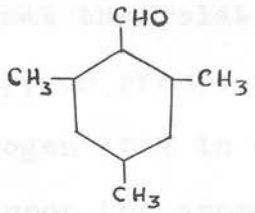
easily undergo the Hofmann degradation to amines and the Curtius reaction to azides without sign of any steric effect:



Carbonyl group.

Steric hindrance to the usual reactions of the -CO group in diortho-substituted ketones has been observed by various workers. Previous workers had shown that with hydroxylamine no oxime was formed by various diortho-substituted methyl ketones - aceto-mesitylene, phenylmesitylketone etc. (Hantzsch, Ber., 1890, 23, 2773; Feith and Davis, Ber., 1891, 24, 3546; Smith, Ber., 1891, 24, 4050, etc.). Kohler and Baltzly (J.A.C.S., 1932, 54, 4015) examined several dimesityl mono- and diketones and found that they, like acetomesitylene, give no oxime, hydrazone or semi-carbazone. Similar steric effects with ketones have been observed in the formation of tertiary alcohols with Grignards, and also in the formation of addition com-pounds with phosphoric acid.

On the other hand, steric effects in reactions of aldehydes are rare. Baum and Meyer (Ber., 1895, 28, 3207; 1896, 29, 836, 2564) found that, unlike acetomesitylene, the corresponding aldehyde



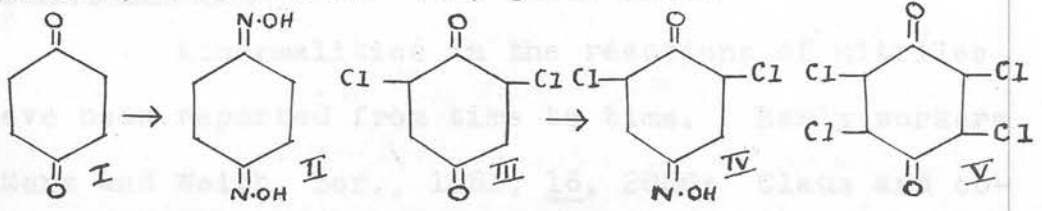
mesityl aldehyde, readily forms an oxime. Similarly, Lock (loc. cit.) obtained, without difficulty, the oxime, hydrazone, bisulphite compound and anil of penta-chlorobenzaldehyde. However, steric effects might have some influence in the Cannizzaro reaction where Weissberger and Haase (J.C.S., 1934, 535) found that certain diortho-substituted aldehydes react more slowly than other isomers.

In the Perkin cinnamic acid synthesis from aldehydes a case of increased reactivity, due to certain ortho-substituents, was observed by Reich (Bull. Soc., (4), 1917, 21, 217). In two hours, at 140 - 150°, the 2:6-dinitro benzaldehyde gave 100% of the acid, the 2:6-dichloro-compound gave 30 - 40%, and the 2:4:6-trimethyl derivative gave none. That is, methyl groups have a greater effect than chlorine atoms, which in turn exert a greater effect than nitro groups. Here, indeed, the chemical nature of the substituent appears to have a considerable influence; the exact nature of this influence is still uncertain since recently it has been shown that chlorine atoms and nitro groups in all positions promote the reaction, and methyl groups in all positions hinder it (Bock, Lock and Schmidt, Mon., 1934, 64, 399). On the whole,

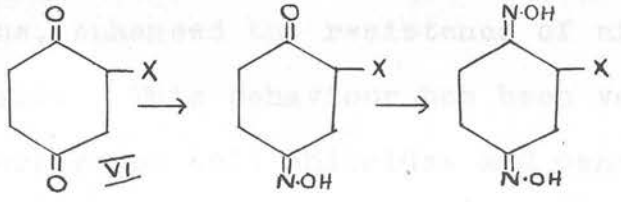
however, it seems that the relatively large "size" of the additional group, or groups, in ketones, compared with the small hydrogen atom in aldehydes, has a decisive influence upon the appearance of hindrance to the carbonyl group.

Oxime formation of quinones.

A remarkably clear-cut case of steric hindrance, showing the relative effect of groups according to their size, was encountered by Kehrmann in the formation of oximes of quinones with hydroxylamine (Ber., 1888, 21, 3315; 1889, 22, 3265). Whereas quinone (I) itself gives a dioxime (II), 2:6-dichloroquinone (III) gives a monoxime (IV), and tetrachloroquinone, or chloranil (V), gives none.



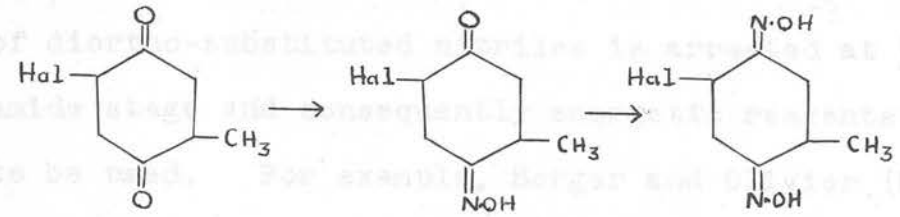
In 2-chloroquinone and toluquinone(2-methyl quinone) (VI) the oxygen atom, having no neighbouring ortho-substituent, is first replaced before the second one reacts.

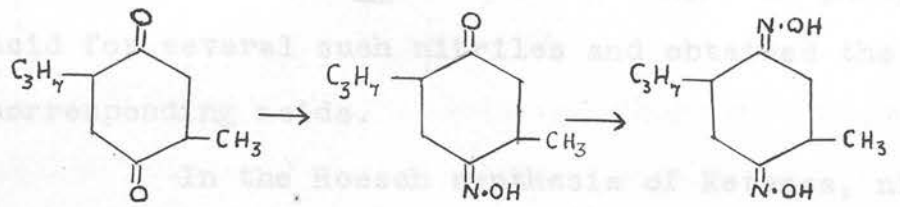


(X = CH_3; Cl)

Again, in the 2:5-disubstituted quinones, containing a methyl group and a halogen, the oxygen ortho to the methyl is first replaced; in those where two alkyls are present in the 2:5 positions, oxygen is first

replaced in the position ortho to the smaller group.





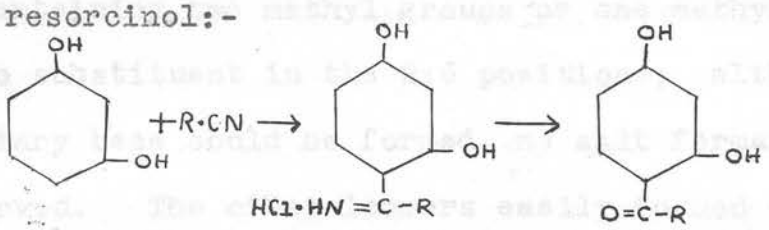
Kehrmann therefore concluded that hindrance in oxime formation is due to the "size" of the groups situated in the ortho position and that the chemical nature of the substituents is of minor importance.

Nitrile group.

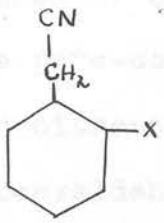
Abnormalities in the reactions of nitriles have been reported from time to time. Early workers (Merz and Weith, Ber., 1883, 16, 2886; Claus and co-workers, Ann., 1891, 265, 378; 266, 225; 1892, 269, 212) found that the introduction of methyl, halogen, or nitro groups in one, and more so in both ortho positions, enhanced the resistance of nitriles to hydrolysis. This behaviour has been verified by those workers on acid chlorides and benzoic acids who used the nitriles as a source of their compounds. Although steric factors predominate in nitrile hydrolysis Küster and Stallberg discovered that the introduction of a meta-nitro group considerably lessened

the resistance to hydrolysis of 2:4:6-trimethyl benzonitrile (see p. 2). In many cases the hydrolysis of diortho-substituted nitriles is arrested at the amide stage and consequently energetic reagents have to be used. For example, Berger and Olivier (Rec. trav. Chim., 1927, 46, 600) used anhydrous phosphoric acid for several such nitriles and obtained the corresponding acids.

In the Hoesch synthesis of ketones, nitriles react with phenols in the presence of ethereal hydrochloric acid and anhydrous zinc chloride as follows, eg. with resorcinol:-

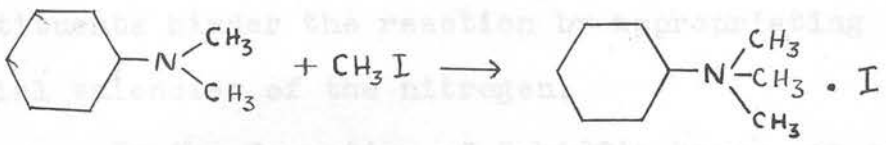


Meta- and para-chlorobenzonitrile react with resorcinol and phloroglucinol in the above manner, but not o-chloro-benzonitrile, nor o-tolunitrile (Orito, Chem. Ztrbl., 1929, II, 1158; Yamashitu, Chem. Ztrbl., 1930, I, 2410; 1933, II, 872). This hindrance can be reduced similarly to that in acid esterification by interposing a $-CH_2$ group between the nucleus and the nitrile grouping. Thus o-substituted phenyl acetonitriles undergo the reaction, albeit to a small extent only.



Amino group.

Tertiary aromatic amines react with methyl iodide to give quaternary ammonium iodides:



In 1872 Hofmann (Ber., 1872, 5, 718) found that even at 150° dimethyl-mesidine gave no such salt. Later, Fischer and Windaus (Ber., 1900, 33, 345, 1907) showed that this behaviour was characteristic of tertiary amines containing two methyl groups or one methyl and one bromo substituent in the 2:6 positions; although the tertiary base could be formed, no salt formation was observed. The other isomers easily formed the salt.

This inability of ortho-substituted aromatic tertiary amines to undergo further additional reactions has also been noted by von Braun (see Ber., 1918, 51, 282, etc.). For example, in the reaction with cyanogen bromide, CN-Br, and iodoacetonitrile, I-CH_2-CN, which ultimately gives quaternary ammonium salts, one ortho-substituent merely hinders the former reagent but completely prevents the latter. It is not quite clear how the presence of ortho methyl groups decreases the velocity of the para-condensations which tertiary amines undergo with nitrous acid to give p-nitroso derivatives, with benzaldehydes to give the triphenyl-methane dyestuffs, and also with diazo-compounds

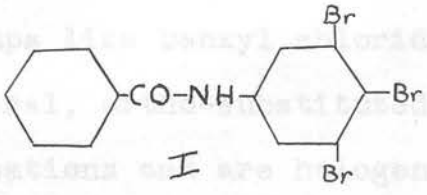
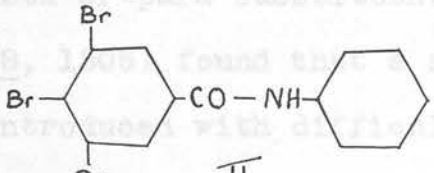
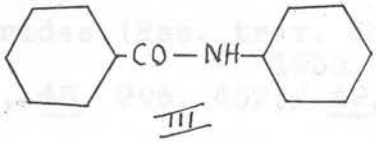
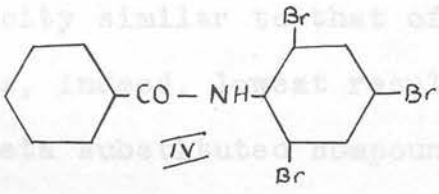
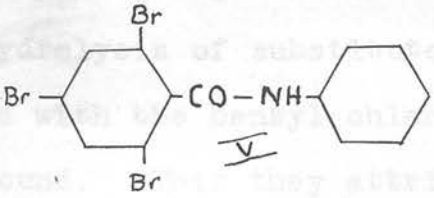
(von Braun, Ber., 1930, 63, 498; 1931, 64, 2465; 1932, 65, 1574 and previous references). von Braun himself is of the opinion that the change takes place in the first phase at the nitrogen atom, and the ortho-substituents hinder the reaction by appropriating the partial valencies of the nitrogen.

In the formation of Schiff's bases, or anils, with aldehydes

$$R - NH_2 + OCH - R' \longrightarrow R - N = CH - R' + H_2O$$

Hantzsch (Ber., 1890, 23, 2776) observed steric hindrance when the base contained ortho-substituents. Thus, sym-tribromoaniline and sym-trinitroaniline, picramide, do not condense with benzaldehyde. But condensation takes place easily when the aldehyde contains the ortho-substituents. For example, 2:6-dinitro-benzaldehyde condenses easily with aniline (Reich, Salzmann and Kawa, Bull. Soc., 1917, 21, 217). Thus the aldehydes do not exhibit hindrance in this reaction. Ortho substituents also have a marked steric effect on the hydrolysis of anils (Reddelien, Ber., 1915, 48, 1462). The formation and hydrolysis of formanilides and acetanilides are likewise hindered.

Recently Asinger (J. pr., 1935, 142, 291) encountered marked steric effects in the hydrolysis of substituted benzanilides. His results are tabulated below:-

Compound.	Time in hours to give 50% hydrolysis.
 I	2
 II	5
 III	16
 IV	215
 V	Unhydrolysed, even after 800 hours.

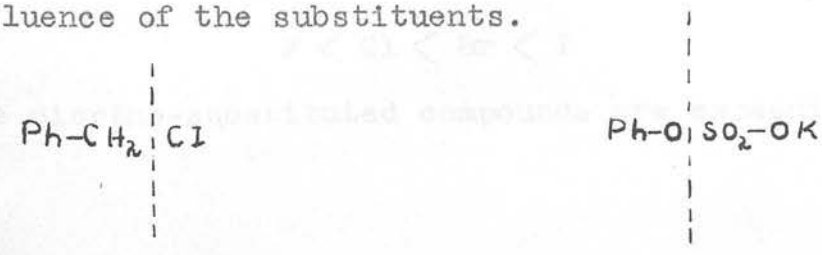
Strong hindrance occurs with the o-o' substituted compounds, especially when the substituents are in the benzene ring next to the -CO group. On the other hand, with the 3:4:5 compounds (I and II) the hydrolysis is

accelerated.

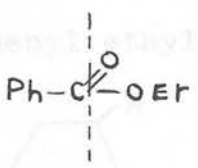
Methyl and halogeno-methyl groups.

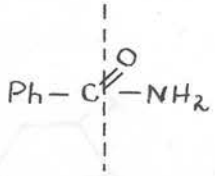
No definite steric effects have been found in the reactions of methyl groups and halogeno-methyl groups like benzyl chlorides or benzal chlorides. In general, ortho-substituted methyl groups undergo condensations and are halogenated as easily as those with meta or para substituents, although Lock (Ber., 1935, 68, 1505) found that a second bromine could only be introduced with difficulty into the $-CH_3$ group of 2:6 dibromotoluene.

Olivier's work on the hydrolysis of benzyl chlorides (Rec. trav. Chim., 1922, 41, 301, 646; 1926, 45, 296, 452; 1930, 49, 697, 996) showed that the ortho-substituted compounds were hydrolysed with a velocity similar to that of their isomers. In some cases, indeed, lowest results were obtained with the di-meta substituted compounds. Recently, Burkhart, Ford and Singleton (J.C.S., 1936, 17) have studied the hydrolysis of substituted aryl sulphuric acids. Here, as with the benzyl chlorides, no steric effects are found. This they attribute to the fact that in both cases the hydrolysis is independent of ortho-substituents, as it takes place at a point removed from the sphere of influence of the substituents.



On the other hand, the hydrolysis of benzoic esters and acid amides, susceptible to ortho-substituents, takes place at the carbon atom next to the nucleus





From a study of the hydrolysis of substituted benzal chlorides Lock and Asinger (Mon., 1932, 59, 152; 1933, 62, 323) found that nitro-groups and chlorine atoms in all positions show an inhibiting effect, whilst methyl groups in all positions accelerate the velocity of hydrolysis. For instance, 2:4:6-trimethyl benzal chloride is hydrolysed 800 times as quickly as the unsubstituted compound. Here the chemical factors would appear to predominate.

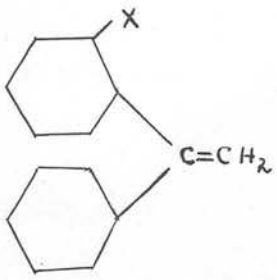
Ethylene group.

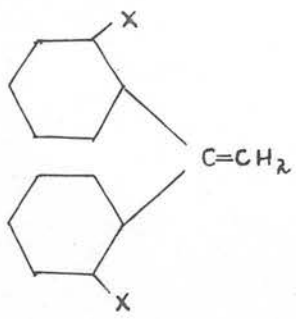
The typical addition reactions of the ethylene group, $-CH=CH-$, in substituted cinnamic acids are hindered by ortho-substituents in the benzene nucleus. Willstaedt (Ber., 1931, 64, 2688) investigated the halogeno-substituted cinnamic acids in their behaviour towards bromine, and found that only ortho-substituents hindered the addition of bromine to the unsaturated $-CH=CH-$ group. The halogens in order of their influence on this reaction are:-

$$F < Cl < Br < I$$

The diortho-substituted compounds are exceedingly

stable to bromine. Bergmann and Bondi (Ber., 1931, 64, 1459; 1933, 66, 287) report steric effects in the addition of phosphorus pentachloride to asymmetric diphenyl ethylenes -





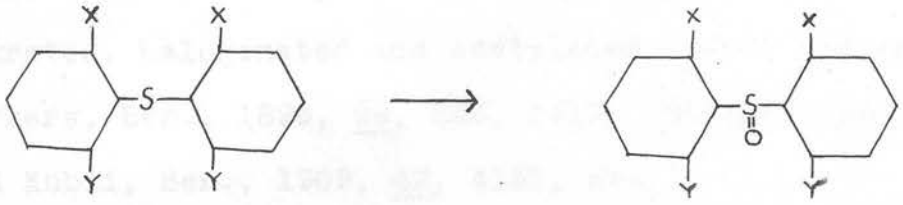
The o-o'-dimethoxy compound adds no PCl_5 and the mono-chloro- and bromo-compounds are very resistant, but the mono-fluoro compound easily reacts.

Auwers (Ber., 1917, 413, 295) also found that o-methyl cinnamic acid only very slowly added on hydrogen bromide. In the reactions quoted it appears that it is the spatial disposition of the ortho-substituents which is influencing the reaction.

Sulphonic group.

Data with reference to steric effects in groups containing sulphur are very scant. Berger and Olivier (Rec. trav. Chim., 1927, 46, 516) mention the hydrolysis of sulphonic acid chlorides, whilst Remsen and Reid mention the corresponding amides (Am. Chem. Jour., 1899, 21, 281), but in neither case was a comparative examination made. With the esters of sulphonic acids Demeney (Rec. trav. Chim., 1931, 50, 71) found that the presence of a nitro group in the benzene ring facilitates hydrolysis, especially so when in

the ortho position. On the other hand, a para-methyl group hinders hydrolysis. Blansksma (Rec. trav. Chim., 1901, 20, 425) showed that the oxidation of diphenyl sulphides to sulphones with nitric or chromic acid



is completely hindered when x = NO_2 and y = CH_3 or CN. Thus both decrease and increase of reactivity, due to substituents, are met with in sulphur compounds also.

Halogens.

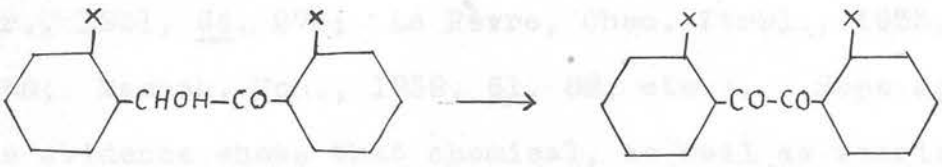
Observations of reduced reactivity in diortho-substituted halogen compounds are very rare. Aceto-acetic ester only reacts very slowly with 2-chloro-1:3-dinitrobenzene (Borsche and Rantzeff, Ann., 1911, 379, 152). Krüger and Bednowa (Chem. Ztrbl., 1933, II, 2123) examined the action of halogeno-benzenes with sodium methylate and found that nitro- and methoxy-groups activate the halogen in the order I > Br > Cl, whilst methyl-, hydroxyl-, and amino-groups usually give rise to decreased activity. Also in reactions like the Ullmann reaction steric effects apparently have no influence. The non-appearance of steric hindrance with halogens gives support to the assumption that an addition compound mechanism is necessary before such effects are to be expected.

Hydrogen.

The nuclear hydrogen atoms in benzene homologues, e.g. mesitylene, on the whole possess increased reactivity. Such compounds are easily nitrated, halogenated and acetylated (Meyer and co-workers, Ber., 1896, 29, 846, 1413; Willstätter, and Kubli, Ber., 1909, 42, 4151, etc.).

Hydroxyl group.

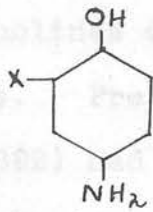
Weissberger and co-workers (Ber., 1932, 65, 1815; Ann., 1930, 478, 119; 1933, 502, 3596) found that the autoxydation of benzoins to benzils in certain cases is retarded by substituents present in the



o-o' positions. It is not yet clear how this hindrance arises or in what phase of the reaction it takes place.

The α-hydroxyl group in alizarin is substituted with difficulty compared with the β-group. Whilst pointing out that this may be due to steric hindrance, Müller (Ber., 1929, 62, 2793) also stresses that the neighbouring carbonyl group is not without effect. Davis (J.C.S., 1900, 77, 33) studied the relative effects of different substituents in the α-position in β-naphthol on the etherification with alcohols and sulphuric acid. Halogen atoms have a big

retarding effect, chlorine being greater than bromine, and the nitro group prevents the etherification entirely. Also Raiford (J.A.C.S., 1924, 46, 2051) found that 2:6 substituents in p-aminophenols (OH = 1) protect the -OH group in acylation to a certain extent, but never completely.



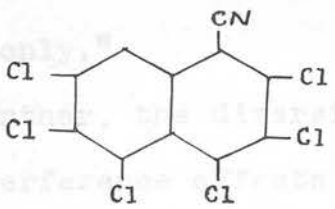
Decreased reactivity in reactions of phenolic hydroxyl groups, and also in the hydrolysis of their methyl ethers and acetyl derivatives, has been reported (Alphen, Rec. trav. Chim., 1930, 49, 158; Schorigin, Ber., 1931, 64, 274; Le Fèvre, Chem. Ztrbl., 1933, II, 3260; Machek, Mon., 1932, 61, 88, etc.). Here again the evidence shows that chemical, as well as steric, factors have to be considered. If, however, phenolic hydroxyl groups are subject to steric influences, the theory put forward (p. 7) that unsaturation is necessary for the appearance of such influences cannot be fundamental. Further work is needed along these lines, however, before the question can be answered.

Steric Effects in Compounds with Condensed Nuclei.

From numerous observations the fact has been brought out that steric effects are exercised by a neighbouring nucleus. This is only to be expected,

since it is now recognised that in α-substituted naphthalenes a group in the 8- or peri-position resembles an ortho-substituent in the benzene series. A brief summary of several reactions bearing this out is given.

Decker (Ber., 1905, 38, 1144) showed 2:8 disubstituted quinolines do not react with methyl iodide or methyl sulphate. Previously Merz and Weith (Ber., 1883, 16, 2886, 2892) had shown that hexachloro-α-naphthonitrile



was remarkably stable to hydrolysis. Then Pinner (Ber., 1890, 23, 2917) found that whereas α-naphthonitrile did not give an imino-ether with alcoholic hydrochloric acid, the β-isomer easily did so. Also in the esterification of naphthoic acids Meyer found that β-substituted α-acids could not be esterified in the cold, whereas the isomeric β-acids behaved like benzoic acid. The results of Davis (p. 26) also showed the difference between α- and β-naphthols.

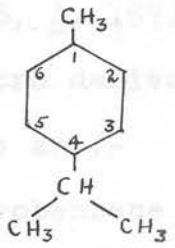
From an examination, therefore, of the extensive literature on the subject, one fact clearly emerges. In considering the effect on a reacting group of neighbouring substituents we must take into

account two properties of the substituent - 1) "Size", 2) Chemical nature. It must be remembered, however, that "size" as applied to a radical or substituent in an organic molecule is a very indefinite term, and the values assigned from physical measurements are in all probability only approximations. Thus Bernal and Crowfoot (Ann.Reps., 1933, 30, 414) emphasise the fact that "molecular distances obtained from X-ray measurements, except where they depend on spectral data for symmetrical diatomic molecules, are of the nature of predictions only."

Further, the diversity in values of the relative interference effects of substituents obtained in two different fields may be pointed out. The order of the relative effects of substituents on the esterification of acids found by Kellas (p. 9) differs considerably from that found by Adams and Yuan in diphenyl work. Thus generalisations in one particular field are not applicable in another field, a fact which complicates a quantitative investigation of steric hindrance.

It has been pointed out recently by Le Fèvre (J.C.S., 1933, 980) that on current theories of benzene substitution the chief factor conducive to reaction at any point is electron availability at that point. Where powerful polar effects enter, such a hypothesis is satisfactory, but where these are weak, as in alkyl groups, it appears to be insufficient. Thus modern

electronic theories indicate that p-cymene



should undergo substitution as easily in position 3 as in 2. But Le Fèvre contends that the chief factor in this case is the bulk of the two alkyl groups, $-CH_3$ and $-CH(CH_3)_2$, and that owing to the greater bulk of the latter, substitution will take place almost exclusively in position 2. In a series of papers (J.C.S., 1934, 840, 1501, 1697) he shows quantitatively that nitration, sulphonation, chlorination, bromination and iodination do take place almost exclusively in that position, thus showing that in this case, at least, the bulk of the groups has a decisive influence on the course of substitution.

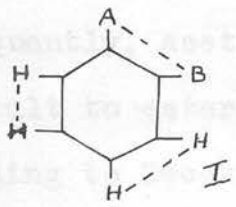
In dealing with powerful polar groups, on the other hand, the course of the substitution appears to depend in certain cases on the electrical nature of the group already present. Fluoro-, chloro-, bromo- and iodo-benzene, on nitration, all give a mixture of the o- and p-nitro derivatives, and if the bulk of the halogen has any hindering effect on this reaction, the largest yield of the o-nitro compound should be obtained with the fluoro-benzene, since fluorine is the smallest of the four halogens. Likewise, iodobenzene should give the smallest yield of the o-nitro derivative, as iodine is the largest halogen. The

opposite proves to be the case, however, as Hollemann (Chem. Rev., 1925, 1, 187) has found that the percentages of o-nitro derivatives given by the four halogeno-benzenes are:-

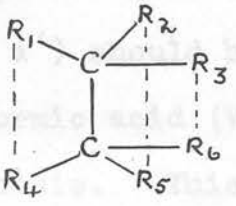
Fluorobenzene	-	12·4%
Chlorobenzene	-	30·1%
Bromobenzene	-	37·6%
Iodobenzene	-	41·1%

In this case the steric factor appears to be of minor importance, the chemical nature of the substituent already present determining the course of substitution.

At present we have no criterion to predict whether or not steric hindrance is to be expected in a reaction. In a recent paper Zwecker (Ber., 1935, 68, 1289) claims to develop such a criterion. In a benzene molecule, I, as in a substituted ethane molecule, II,



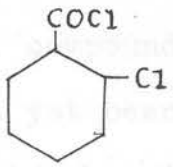
I



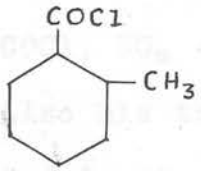
II

he postulates that intramolecular forces are at work after the fashion of residual valencies. These are indicated by the dotted lines. Continuing, he affirms that the behaviour of the benzene molecule, I, may be forecasted by a knowledge of the properties of what he calls the "substituent pair", AB, and vice

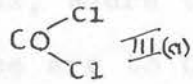
versa. In some cases, AB is not merely a hypothetical compound but can be isolated, and the theory may be applied. For instance, with the acid chlorides,



III



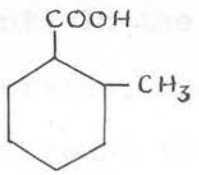
IV



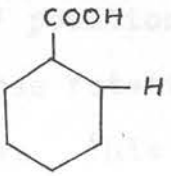
III(a)

CH_3-COCl IV(a)

where phosgene, $CO(Cl)_2$, and acetyl chloride, $CH_3 - COCl$, are the corresponding "substituent pairs", the difference in hydrolysis of o-chloro benzoyl chloride (III) and o-methyl benzoyl chloride (IV) is comparable to that between phosgene (III a) and acetyl chloride (IV a). The o-chloro compound is more slowly hydrolysed than the corresponding methyl derivative, and phosgene is more resistant to hydrolysis than acetyl chloride. Similarly, o-toluic acid (V) is more difficult to esterify than benzoic acid (VI); consequently, acetic acid (V a) should be more difficult to esterify than formic acid (VI a) according to Zwecker's hypothesis. This is the case.



V



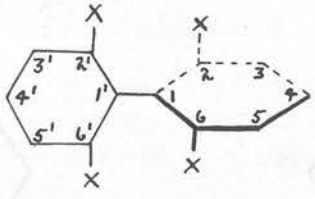
VI

CH_3-COOH V(a) $H-COOH$ VI(a)

In several other cases his theory is well

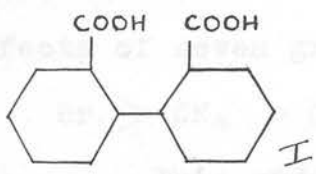
borne out, but at present the theory is incapable of a really comprehensive application, since in many cases his "substituent pairs" are unknown. For example, compounds like NO_2 - COCl, NO_2 - $CONH_2$ etc. have not yet been isolated. Also his theory tells us nothing of what is to be expected in diortho-substituted compounds, where the most typical cases of steric hindrance are to be found.

The theory that substituent groups in an organic molecule can provide a mechanical blocking receives strong support from the study of isomerism due to restricted rotation about a single bond. In the diphenyl series the collapse of the Kaufler folded structure theory and the examination of resolvable and non-resolvable compounds led to certain conclusions which are now generally accepted.

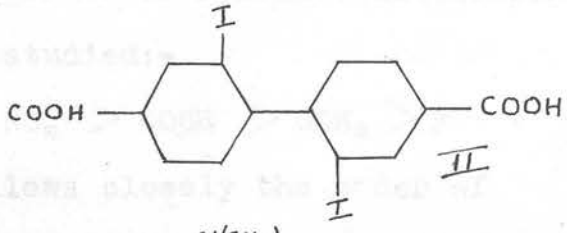


Essentially the theory put forward by various workers for the isomerism in the diphenyl series is that substituents in the 2, 2', 6, 6' positions can, by their interference, restrict the free rotation of the two nuclei around the common axis. This prevents the rings from becoming co-planar, and thereby produces in the molecule an asymmetric configuration. Thus the molecule displays optical activity and can be resolved into optical enantiomorphs. Compounds with

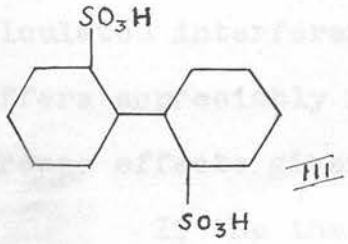
only three of the four above positions occupied also exhibit this phenomenon. At first it was thought that the presence of three groups in the ortho positions was the minimum requirement to produce steric blocking. But it was pointed out that, if sufficiently large, two ortho-substituents might suffice. This has been confirmed experimentally. Thus, diphenic acid (I) is not resolvable. But 2-2'-Di-iodo-4:4'-dicarboxy diphenyl (II) (Searle and Adams, J.A.C.S., 1933, 55, 1649), diphenyl-2:2'-disulphonic acid (III) and the methiodide of 2:2'-bisdimethylamino-diphenyl (IV) have all been resolved, showing that two groups, if sufficiently large, can prevent free rotation in the diphenyl system.



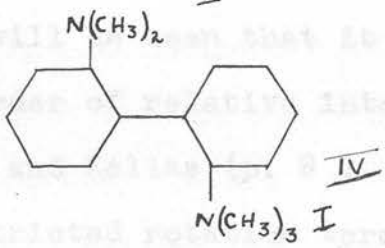
I



II



III



IV

III was resolved by Lesslie and Turner (J.C.S., 1932, 2394) and IV by Turner (Chem. and Ind., 1932, 51, 435).

In the appearance of optical activity in the diphenyl series it appears that steric factors predominate and that electrical factors are of minor importance. Considering diphenyl molecules in which all four ortho-substituents are identical, Adams and Yuan (Chem. Rev., 1933, 12, 305) found that the rates

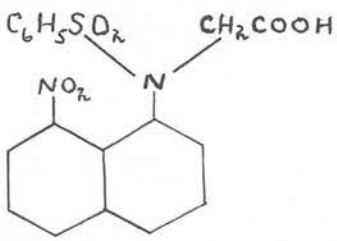
of racemisation vary, not with the electrical nature of the substituents, but with their size. Compounds with four chlorines or four nitro groups, which are polar in character, were very resistant to racemisation. But the compound with four methyl groups, essentially non-polar and approximately the same size as the chlorines, was also very resistant to racemisation. On the other hand, the tetrafluoro and tetramethoxy compounds were not resolvable. These authors contend that, by considering all compounds studied, it is impossible to correlate electrical nature and interference effects of the individual groups.

From other racemisation experiments (loc. cit., p. 299) they give as the order of relative interference effects of seven groups studied:-

$$Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F$$

This order follows closely the order of calculated interference. It will be seen that it differs appreciably from the order of relative interference effects given by Meyer and Kellas (p. 9).

If the theory of restricted rotation were true in the diphenyl system, other authors predicted that the phenomenon should be exhibited by other ring systems. This has proved to be the case. Thus Mills and Elliott (J.C.S., 1928, 1291) resolved the naphthalene compound



This was explained by these authors as molecular asymmetry due to restricted rotation about the C - N bond because of the collision of the groups attached to the nitrogen atom and the $-NO_2$ group in the 8 position. To support this no optical activity was shown by the non-nitrated compound. Other similar examples have been found. Adams and co-workers have also found this inhibition of rotation in systems related to the diphenyl system, e.g., the phenyl-pyrrole and dipyrryl systems.

Summary.

In considering the reactivity of a functional group as affected by other substituents, two factors must be taken into account:

a) The bulk of the substituent.

b) Its chemical or electronic nature.

In many cases, chiefly with ortho-substituents, a decrease in reactivity occurs. This is attributed to the influence of the first factor.

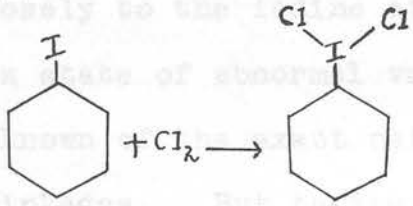
On the other hand, the fact that the presence of substituents often leads to an enhanced reactivity emphasises the point that the chemical or electronic nature of substituents cannot be neglected.

Although clear-cut cases of steric hindrance have been observed, generalisations made in one sphere of the problem cannot be applied without reserve to

to other spheres. Data obtained in different fields are often conflicting, and thus quantitative measurements in one particular field are complicated.

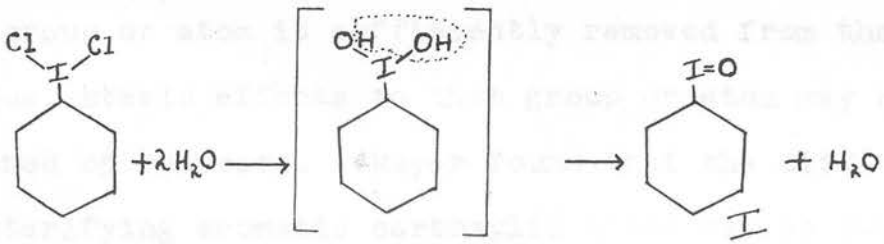
The present thesis is concerned chiefly with a quantitative study of the formation of the aromatic iodo-chlorides.

As far back as 1886 Willgerodt (J. pr., (2),1886, 33, 154) made the discovery that under ordinary conditions chlorine does not displace iodine in iodobenzene, but forms an addition compound, phenyl iodo-dichloride:-



In this compound the chlorine atoms are very reactive, displacing iodine from potassium iodide solution.

The iodo-chlorides have proved to be the basis of an interesting series of compounds in which the iodine atom exhibits abnormal valency. Thus by the action of alkalis, phenyl iodo-chloride yields iodoso-benzene (I), presumably due to replacement of the chlorine atoms by hydroxyl groups with subsequent removal of a molecule of water from the unstable di-hydroxy compound so formed.



By oxidation of iodoso-benzene iodoxy-benzene, $Ph\text{-}IO_2$, is formed.

Meyer and Hartmann (Ber., 1894, 27, 426) found that in presence of moist silver oxide iodosobenzene and iodoxy-benzene react to form diphenyliodonium hydroxide (II), a compound which resembles ammonium hydroxide in its basic properties.

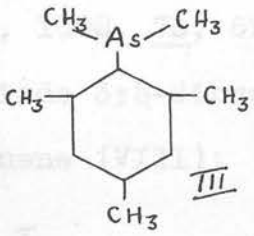
$$Ph - IO + Ph - IO_2 + AgOH \longrightarrow (Ph)_2I - OH + AgIO_3$$

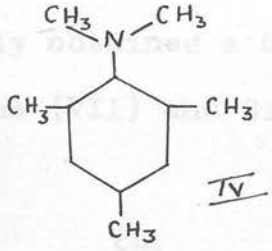
II

Beyond the fact that the chlorine atoms are attached loosely to the iodine atom, which is presumably in a state of abnormal valency, practically nothing is known of the exact nature of the chlorine to iodine linkages. But taking as a basis that the formation of the aromatic iodo-chlorides represents an addition reaction, the present research is an attempt to find out whether or not the reaction is subject to steric hindrance. Indications are that the "size" of the iodine atom is sufficient to take it outwith the sphere of influence of neighbouring substituents. It was therefore to be expected that the formation of the iodo-chlorides would not be subject to the ordinary steric hindrance rules.

Evidence is to hand in the literature that if a group or atom is sufficiently removed from the nucleus, steric effects to that group or atom may be lessened or overcome. Meyer found that the difficulty in esterifying aromatic carboxylic acids may be overcome by interposing a $-CH_2$ group between the nucleus and the -COOH group (p. 10). Similarly, Orito and

Yamishitu (p. 18) showed that steric effects in the Hoesch ketone synthesis from nitriles are considerably lessened by removing the -CN grouping from the nucleus. Again, Burkhardt, Ford and Singleton pointed out (p. 22) that hydrolysis of benzyl chlorides and aryl sulphuric acids takes place at a point so far removed from the nucleus as to make the reaction in both cases non-susceptible to the steric effects of ortho-substituents. In a recent paper Lesslie and Turner (J.C.S., 1933, 1589) report that diortho-substituted tertiary arsine compounds containing the $-As(CH_3)_2$ group are much more reactive than the corresponding nitrogen derivatives. For example, trimethyl-phenyl dimethylarsine (III) easily adds on methyl, and even ethyl iodide at 0°C., whilst N-dimethyl mesidine (IV) does not do so at 150°C. (cf. p. 19).

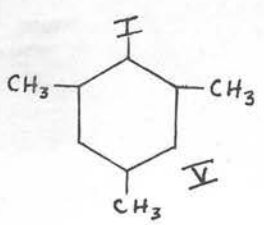




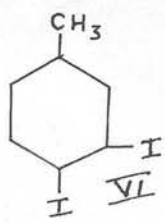
The above authors attribute this difference in behaviour towards alkyl iodides to the fact that in the IV/arsenic atom (radius 1·2 Å) is easy of access compared with the nitrogen atom (radius 0·71 Å) which is sheltered by the neighbouring ortho-substituents (see Diagram I).

The researches of Willgerodt and his co-workers pointed to the fact that the presence of a

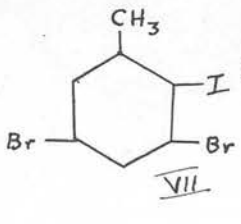
negative group or atom, such as Br, Cl, NO_2 , and SO_3H, in any position in the benzene ring, does not prevent the formation of the iodo-chlorides. Similarly, positive alkyl groups, $-CH_3$, $-C_2H_5$, $-C_3H_7$ and $-C_4H_9$, etc. apparently had no effect (Willgerodt, Ber., 1893, 26, 1532, 1802; Willgerodt and Brandt, J. pr., 1904, 69, 433; Willgerodt and Dammann, Ber., 1901, 34, 3678; Willgerodt and Rampocher, Ber., 1901, 34, 3666). However, with iodo-mesitylene (V) Willgerodt and Roggatz (J. pr., 1900, 61, 423) found that the dichloride was difficult to obtain and was unstable. Although, in general, di-iodo compounds give a tetrachloride, Willgerodt and Simonis (Ber., 1906, 39, 269) discovered that 3:4-di-iodotoluene (VI) only formed a dichloride. This, they state, may be due to steric causes. On the other hand, McCrae (J.C.S., 1898, 73, 691) easily obtained a dichloride from 2-iodo 3:5-dibromotoluene (VII) and 2:4:6-tribromo-iodotoluene (VIII).



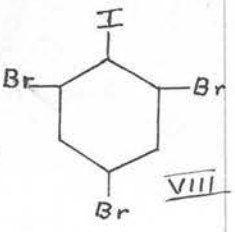
V



VI



VII



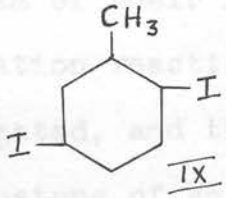
VIII

All previous work, however, has been merely qualitative. Consequently, an effort has been made to obtain quantitative data.

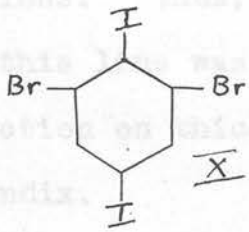
From figures given by Boys (Proc. Roy. Soc., 1934, 144, 683) for the radii and volumes of atoms

and radicals, a diagram was drawn representing an iodo-benzene molecule in which bromine atoms occupy the ortho-positions, and is here appended. The hydrogen atoms are omitted for clarity. The radii of the atoms are iodine 1·35 Å, bromine 1·13 Å, carbon 0·77 Å. Examination of the diagram shows that the iodine atom is indeed considerably removed from the comparatively large bromine substituents (see Diagram II).

The iodo-compounds studied were chiefly mono- and diortho-substituted benzene compounds. Where unknown, the iodo-chloride was isolated in a pure state and examined for melting point, etc. In two cases, 2:5-di-iodotoluene (IX) and 1:4-di-iodo 2:6 di-bromo-benzene (X), an examination was carried out to see if the unsubstituted iodine atom exhibited any difference to the iodine atom with neighbouring substituents.



IX



X

Then the research was extended to naphthalene derivatives in order to see if α-iodo naphthalenes showed any differences to the β-iodo isomers.

Also, since these naphthalene derivatives were obtained from the corresponding amines, a summary examination was made of the hydrolysis of α- and β-acetamino compounds. This was merely qualitative.

In the experimental section the method of

isolation of the iodo-chlorides is given, together with the typical method of analysis of the pure compound. The quantitative method used is then described, followed by a listed preparation of the compounds studied. The figures for the quantitative experiments are quoted after each preparation and are summarised by means of tables at the conclusion of the experimental section on iodo-chlorides.

It was thought of interest to extend the research to other groups containing a large atom, and consequently the sulphur atom (radius 1·06; Boys, loc. cit.) suggested itself. Therefore an examination was commenced of the aromatic thiobenzoic acids of the general formula, R - COSH. But it was recognised that this problem is beset with difficulties, due to the instability of the acids and the uncertainty of the mechanism of their reactions. Thus, except for a few condensation reactions, this line was not thoroughly investigated, and the section on thio-acids is rather in the nature of an appendix.

E X P E R I M E N T A L.

Isolation of the Iodo-chlorides.

The method used for the isolation of the iodo-chlorides was that described by Willgerodt. It is the general method and has been widely used by various workers.

The method consists in passing a stream of dry chlorine gas into a chloroform solution of the iodine compound; cooling of the chloroform solution to 0°C. is generally to be recommended. The iodo-chloride separates in characteristic yellow crystals, but in some cases it is necessary to concentrate the solution before separation occurs. This is due to the appreciable solubility in chloroform of some iodo-chlorides.

In almost every case recorded in the literature the iodo-chloride is yellow in colour. With one compound in this work, however, a red dichloride was obtained.

Generally the iodo-chlorides do not show a sharp melting point but decompose over a range of 2 - 3°C. with evolution of gas.

Analysis of the Iodo-chlorides.

For analysis of these compounds advantage is

taken of the ease with which they displace iodine from potassium iodide solution according to equation (a):-

$$RICl_2 + 2KI \longrightarrow RI + 2KCl + I_2 \quad (a)$$

The iodine liberated is then determined by titrating with standard sodium thiosulphate solution:-

$$I_2 + 2Na_2S_2O_3 \cdot 5H_2O \longrightarrow 2NaI + Na_2S_4O_6 + 5H_2O \quad (b)$$

From equations (a) and (b) we obtain the relationship 596·4 g. $Na_2S_2O_3 \cdot 5H_2O \equiv$ 254 g. $I_2 \equiv$ 71 g. "active" Cl_2, or 1000 c.c. N sodium thiosulphate solution $\equiv$ 127g. $I_2 \equiv$ 35·5 g. Cl_2. Thus 1 c.c. N/100 sodium thiosulphate solution $\equiv$ 0·000355 g. "active" Cl_2. The percentage of "active" chlorine can then be found from the equation:-

$$\% Cl_2 = \frac{a \times 0{\cdot}000355 \times 100}{b}$$

where a = volume of N/100 thiosulphate solution required;

b = weight of dichloride used.

Detailed method of analysis.

A known weight (0·02- 0·05g.) of the dichloride was taken and added to a solution of potassium iodide to which 1 c.c. of dilute acetic acid had been added. It was also found that the addition of a few c.c. of chloroform assisted in the liberation of the iodine; otherwise, complete decomposition of the iodochloride was retarded.

A brown colouration of iodine developed and

N/100 sodium thiosulphate solution (accurately made up to that strength) was added. The flask containing the iodide solution was shaken during this addition. Towards the end of the titration, 1 c.c. of a starch solution was added and addition of the thiosulphate solution continued until the blue colouration had disappeared. (The colouration at this point graduates from deep blue through pale purple to a colourless solution. Care must be taken, as the bluish coloura-tion often reappears on agitation for several seconds). With care, sharp end-points were obtained.

Description of quantitative experiments.

The iodo-chlorides differ appreciably in their solubility towards chloroform. Therefore filtration from chloroform solution of the dichloride formed in a given time can only give a very rough idea of the percentage formation. A general quantitative method had therefore to be evolved. This is described below.

A known weight (about 0·5 g.) of the iodine compound was dissolved in 10 c.c. chloroform in a 100 c.c. flask fitted with a cork carrying a water-condenser and an inlet tube for chlorine. The solution was cooled to 0°C. by surrounding the flask with an ice-salt mixture. A stream of dry chlorine gas from a cylinder was then passed in at a uniform rate for 30 minutes. Care was taken to maintain the

temperature of 0°C. throughout all the experiments, and also to keep the bubbling of chlorine as constant as possible.

After 30 minutes the solution, plus any precipitate, was carefully transferred to a small beaker, the last traces of solid being washed out of the flask with a few c.c.'s of chloroform. The solvent was then removed by blowing through the solution a current of dry air; this procedure also served to remove any free chlorine. In almost every case, especially where the original iodo-compound is a solid, this procedure gave a clean dry precipitate. This was intimately mixed with a glass rod and portions of it, of known weight, were added to potassium iodide solution. The volume of N/100 thiosulphate solution required for neutralisation of the iodine liberated was then determined. From this volume the quantity of dichloride present in the portion was calculated and, knowing the weight of the portion used, the percentage of dichloride was found.

Example:-

Suppose we are dealing with the compound, $C_6H_4(NO_2)ICl_2$, whose gram-molecular weight, 320, contains 71 g. "active" chlorine, and we find that portions (X g.) of the dichloride precipitate require 18·5 c.c. N/100 thiosulphate solution for neutralisation.

Now 320 g. dichloride contains 71 g. $Cl_2 \equiv$ 596·4 g,

thiosulphate.

Therefore 2000 c.c. N thiosulphate solution $\equiv$ 71 g. $Cl_2 \equiv$ 320 g. dichloride.

Or 20 c.c. N/100 thiosulphate solution $\equiv$ 0·0320 g. dichloride.

Thus the weight of dichloride present in X g. of precipitate $= \frac{0{\cdot}0320 \times 18{\cdot}5}{20}$ g.

Knowing X, the percentage of dichloride present in the precipitate can be calculated.

In all cases the experiments were duplicated to obtain constant results.

With some iodo-compounds it was found that the precipitate obtained on evaporation of the solvent remained in a semi-solid state - presumably due to the presence of unchanged iodo-compound. In these cases it was found advisable to start with a larger weight of the iodo-compound and also to titrate the total semi-solid precipitate against N thiosulphate solution. Thus, knowing the amount of dichloride obtained, and the amount to be expected on theory, the percentage formation was calculated.

A summary of the percentages obtained from various iodo-compounds is given in two tables at the end of this section - one for benzene and one for naphthalene derivatives. This is preceded by the preparation of the iodo-compounds examined. The experimental figures for each individual compound are

included at the end of each preparation, and where the dichloride has not been listed in the literature its preparation, analysis and melting point are recorded. Where already known, only the original reference is quoted.

All new intermediate compounds were analysed. The Micro-Dumas method was used for those compounds containing nitrogen. For halogen compounds the hydrogenation method of Ter Meulen and Hessingla (Thorpe and Whiteley: "Manual of Organic Chemical Analysis", p. 275) was employed. In most cases the isolation and analysis of the dichloride gave an added check to the identification of new iodine compounds.

The melting points quoted are all corrected, being determined by means of a thermometer calibrated against standard short-stem thermometers.

BENZENE DERIVATIVES.

Iodobenzene.

Iodobenzene was prepared in 80% yield by the method described in Organic Synthesis, 9, 46.

B.p. 184 - 186°C.

Dichloride (Willgerodt, J. pr., 1886, 33, 155).

Quantitative experiment:

In this case the quantity of dichloride in the total precipitate was determined, using N sodium thiosulphate solution. 1·086 g. iodobenzene gave a precipitate which required 10·65 c.c. of N sodium thiosulphate solution.

But 20 c.c N/100 thiosulphate ≡ 0·0275 g. dichloride.

Therefore weight of dichloride =

$$\frac{0{\cdot}0275 \times 100 \times 10{\cdot}65}{20} \text{ g.}$$

= 1·464 g. dichloride.

But 1·086 g. iodobenzene should give $\frac{275 \times 1{\cdot}086}{204}$ g. dichloride = 1·464 g. dichloride.

Therefore percentage formation = 100%.

o-Iodotoluene.

o-Iodotoluene was prepared by the method described in Cohen, "Practical Organic Chemistry", 1924, p. 190, for the p-derivative.

25 g. o-toluidine

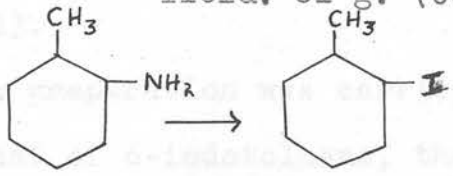
25 g. (13·5 c.c.) conc. sulphuric acid in 125 c.c. water

10 g. sodium nitrite in 20 c.c. water

30 g. potassium iodide in 50 c.c. water.

The procedure followed was exactly as described in Cohen, except that instead of steam-distilling the product, a distillation in vacuo was carried out after extraction with ether. A colourless oil came over at 88°C. under a pressure of 18 mm. It developed a reddish tint on standing.

Yield: 31 g. (60%).



Dichloride. (Willgerodt, Ber., 1893, 26, 360 ; Caldwell and Werner, J.C.S., 1907, 91, 249 ; Lucas, Kennedy and Wilmot, J.A.C.S., 1936, 58, 159).

Quantitative.

0·5 g. were dissolved in 10 c.c. chloroform and chlorine was passed in for 30 minutes. No precipitate was obtained and the solvent was removed. From the precipitate thus obtained, 0·0391 g. required 26·10 c.c. N/100 thiosulphate solution, equivalent to

$$\frac{0{\cdot}0289 \times 26{\cdot}10}{20} \text{ or } 0{\cdot}03771 \text{ g. dichloride}$$

Therefore percentage of dichloride = $\frac{0{\cdot}03771 \times 100}{0{\cdot}0391}$

= 96%.

Note:- In the above cases the experimental figures are given in detail to show the application of the method. All other experiments are only given briefly, and unless otherwise stated the procedure was as recorded for o-iodotoluene - that is, using 0·5 g. substance and analysing with N/100 thiosulphate solution.

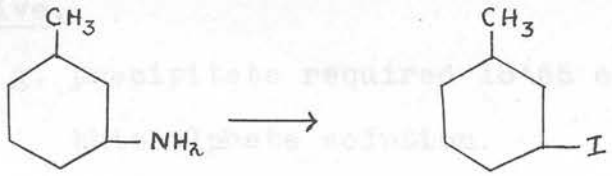
m-Iodotoluene.

(Cohen, p. 190).

This preparation was carried out exactly the same as that of o-iodotoluene, the oil obtained being purified by vacuum distillation. Similar quantities were used.

Yield: 25 g. (50% theory)

B.p. 110°C./30 mm.



Dichloride. (Willgerodt and Umbach, Ann., 1903, 327, 269 ; Caldwell and Werner, loc. cit.).

Quantitative.

0·0340 g. precipitate required 21·4 c.c. N/100 thiosulphate solution.

Therefore percentage dichloride = $\frac{0{\cdot}0289 \times 21{\cdot}4 \times 100}{20 \times 0{\cdot}0340}$

= 91%.

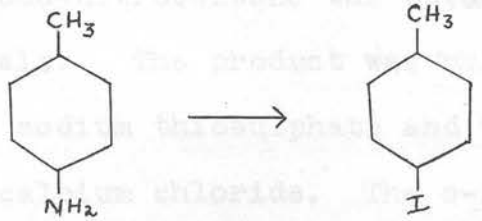
p-Iodotoluene.

(Cohen, p. 190).

Similar quantities were used as for the o- and m-derivatives. In this case, however, the product was steam-distilled from the reaction mixture and solidified in the receiver. It was purified by recrystallising from alcohol, separating in colourless plates from this solvent.

Yield: 37 g. (75%)

M.p. 34°C.



Dichloride. (Willgerodt, Ber., 1893, 26, 358 ; Caldwell and Werner, loc. cit.).

Quantitative.

0·0299 g. precipitate required 18·55 c.c. N/100 thiosulphate solution.

Percentage dichloride = $\frac{0{\cdot}0289 \times 18{\cdot}55 \times 100}{20 \times 0{\cdot}0299}$

= 90%.

o-Iodo-nitrobenzene.

(Uhlmann, Ber., 1896, 29, 1880).

15 g. o-nitraniline

22·5 g. conc. sulphuric acid in 125 c.c. water

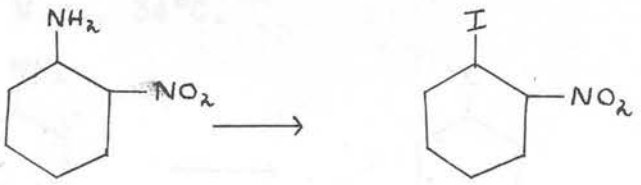
7·5 g. sodium nitrite

30 g. potassium iodide in 100 c.c. water.

The o-nitraniline was dissolved in the sulphuric acid solution and diazotised with the sodium nitrite dissolved in the minimum of water. This diazo solution was added drop by drop to the warm solution (60°C.) of potassium iodide. After cooling, the crude iodo-nitrobenzene was obtained as small brown crystals. The product was extracted with ether, washed with sodium thiosulphate and water, and finally dried over calcium chloride. The o-iodo-nitrobenzene was obtained as a pale yellow solid on distilling under reduced pressure. (B.p., 288 - 289°C./729 mm.).

Yield: 22 g. (85% theory).

M.p., 49·5 - 50°C.



Dichloride (Willgerodt, Ber., 1893, 26, 1809)

Quantitative:

0·0557 g. precipitate required 24·2 c.c. N/100 thiosulphate solution

$$\text{Percentage dichloride} = \frac{0{\cdot}0320 \times 24{\cdot}2 \times 100}{20 \times 0{\cdot}0557}$$

$$= 70\%.$$

m-Iodo-nitrobenzene.

(Uhlmann, loc. cit.)

15 g. m-nitraniline

45 g. conc. sulphuric acid in 250 c.c. water

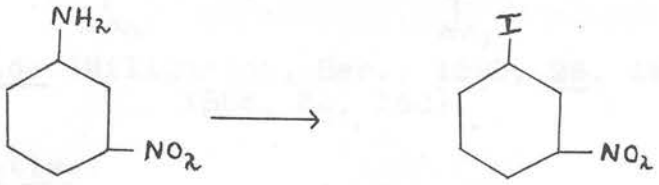
7·5 g. sodium nitrite

30 g. potassium iodide in 100 c.c. water.

The diazo solution of the m-nitroaniline was slowly added to a boiling solution of potassium iodide. On cooling, the meta-iodo-nitrobenzene separated as an oil which was extracted with ether and treated as in the case of the ortho-isomer. The crude product was distilled under reduced pressure, b.p. 135 - 136°C./13 mm. When pure it was obtained as a pale yellow solid.

Yield, 15 g. (56·5% theory)

M.p., 34°C.



Dichloride (Willgerodt, Ber., 1893, 26, 1311).

Quantitative:

0·0545 g. precipitate required 33·4 c.c. N/100 thiosulphate solution.

$$\text{Percentage dichloride} = \frac{0{\cdot}0320 \times 33{\cdot}4 \times 100}{20 \times 0{\cdot}0545}$$

$$= 98\%.$$

p-Iodo-nitrobenzene.

(Uhlmann, loc. cit.)

Similar quantities to those employed in the preparation of o-iodo-nitrobenzene were used. The potassium iodide solution was maintained at a temperature of 40 - 45°C. during addition of the diazo solution. The crude product (22 g.)was filtered off and washed with potassium iodide solution and then with water. The p-iodo-nitrobenzene was recrystallised from alcohol (once), then from acetone (twice), being obtained as a pale buff-coloured powder.

Yield, 17·5 g. (66% theory).

M.p., 71·5°C.

Dichloride (Willgerodt, Ber., 1893, 26, 362 ; J. pr., 1886, 33, 160).

Quantitative:

0·0460 g. precipitate required 25·75 c.c. N/100 thiosulphate solution.

$$\text{Percentage dichloride} = \frac{0{\cdot}0320 \times 25{\cdot}75 \times 100}{20 \times 0{\cdot}0460}$$

$$= 90\%.$$

Iodo-mesitylene.

(a) Nitro-mesitylene.

(Org. Synth., 14, 68).

40 g. mesitylene

60 g. (55·5 c.c.) acetic anhydride

31·5 g. (20·8 c.c.) fuming nitric acid (S.G. 1·51)

20 g. (19·1 c.c.) glacial acetic acid

20 g. (18·5 c.c.) acetic anhydride.

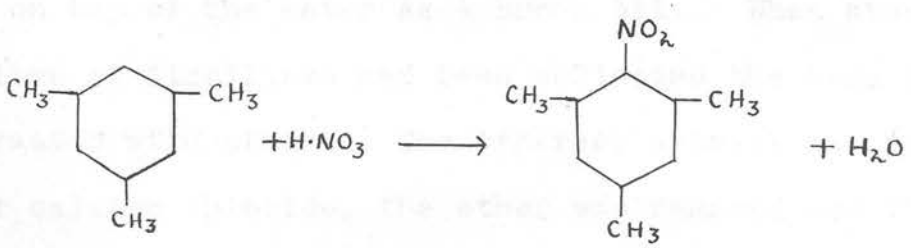
Mesitylene (40 g.) and acetic anhydride (55·5 c.c.) were placed in a 500 c.c. three-necked, round-bottomed flask provided with a mechanical stirrer, dropping funnel and thermometer. The mixture was cooled, and when below 10°C. a mixture of fuming nitric acid (20·8 c.c.) in glacial acetic acid (19·1 c.c.) and acetic anhydride was added (18·5 c.c.).* The nitrating mixture was added, with constant stirring, over a period of 40 minutes, the temperature being maintained between 15 - 20°C. After standing for two hours at room temperature, the contents of the flask

* The nitric acid should be added cautiously to the acetic acid - acetic anhydride solution, keeping the temperature below 20°C.

were heated, with shaking, to 50°C. and maintained there for 10 minutes, cooled and poured into water (800 c.c.). Sodium chloride (40 g.) was added and this mixture was well stirred. The aqueous layer was decanted and extracted with ether (220 c.c.). This ethereal extract was added to the residual nitro-mesitylene, and the solution washed with 30 c.c.-portions of a 10% sodium hydroxide solution until the water extract was distinctly alkaline. The ether was removed on the steam-bath, 150 c.c. 10% sodium hydroxide was added, and the mixture was steam-distilled until no oily drops came over. About 1500 c.c. of distillate were collected; most of the water was decanted from the nitro-mesitylene which had solidified and settled to the bottom of the receiver. The nitro compound was extracted with ether (30 c.c.) and dried over $CaCl_2$. On evaporating off the ether, the nitro-mesitylene solidified quickly in large pale-yellow plates which were not purified further.

Yield, 47 g. (87%).

M.p., 43 - 44°C.



(b) Mesidine.

(cf. Fittig and Storer, Ann., 1868, 147, 3)

The reduction was carried out by a method based on that for the reduction of nitrobenzene to aniline described by Gattermann and Wieland ("Lab. Methods in Org. Chem." 1932, p. 156).

41·25 g. nitro-mesitylene

60 g. granulated tin

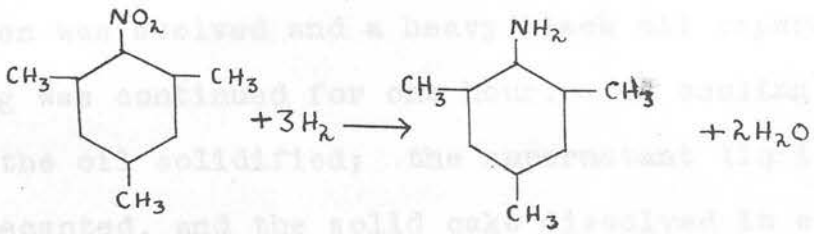
135 c.c. conc. hydrochloric acid.

Concentrated hydrochloric acid (135 c.c.) was added in portions to a mixture of nitro-mesitylene (41·25 g.) and finely granulated tin (60 g.) in a litre round-bottomed flask fitted with an air condenser. No reaction took place in the cold, however, and when all the acid had been added the flask was heated cautiously on the water-bath. A somewhat vigorous reaction set in after half-an-hour and a solid separated. Heating was continued for two hours, water (50 c.c.) was added, and then sodium hydroxide (75 g.) dissolved in water (150 c.c.) was introduced, and the mixture was immediately steam-distilled. The free base distilled over, collecting on top of the water as a brown oil. When about 1 litre of distillate had been collected the base was extracted with ether. The ethereal extract was dried over calcium chloride, the ether was removed and the brown oil was distilled, using an air condenser.

Practically all came over at 232° (corrected) as a pale yellow oil.

Yield, 29 g. (80%).

B.p., 232°C.



(c) Iodo-mesitylene.

Tohl (Ber., 1892, 25, 1522) records the preparation of this compound by the diazotisation of mesidine but with no detail or yield. It was here obtained in quite good yield by the diazotisation of mesidine hydrochloride.

10 g. mesidine

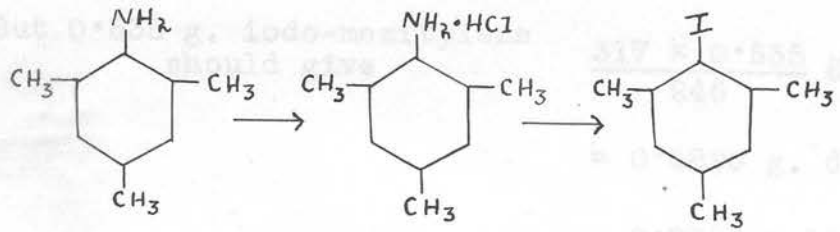
220 c.c. dilute hydrochloric acid

6·8 g. sodium nitrite in 30 c.c. water

20 g. potassium iodide in 100 c.c. water

Mesidine (10 g.) was added slowly, with stirring, to dilute hydrochloric acid (220 c.c.) when the salt of the base separated in the form of a fine suspension. The mixture was cooled to 0°C. and sodium nitrite (6·8 g.) in water (30 c.c.) was added, with stirring, until nitrous acid was shown in excess by starch-iodide

paper. A little urea was added to destroy the slight excess of nitrous acid, the solution was filtered and stirred into potassium iodide solution (20 g. in 100 c.c. water). A reddish colour was evolved and after half-an-hour the mixture was heated on the steam-bath. Nitrogen was evolved and a heavy black oil separated; heating was continued for one hour. On cooling overnight the oil solidified; the supernatant liquid was then decanted, and the solid cake dissolved in ether. This ethereal solution was well washed with alkali to remove any phenol formed, and then dried over calcium chloride. The ether was removed on the steam-bath and the brown oil thus obtained was distilled in vacuo. Under a pressure of 20 mm. a light brown oil came over at 140 - 145°, crystallising in the receiver. The solid was dried by pressing between filter papers giving colourless crystals of M.p. 30°. The yield was 11 g. (60%)



Dichloride.

Willgerodt and Roggatz (J. pr., 1900, 61, 423) found that the dichloride of iodo-mesitylene was only obtained with difficulty by passing chlorine into a chloroform solution of iodo-mesitylene. They report that strong external cooling is required to prevent

nuclear chlorination of the iodo-mesitylene. Also, when obtained, the dichloride and its iodoso-derivative are extremely unstable.

The present work bears this out, as it was shown that the dichloride was only obtained in small yield under the conditions employed.

Quantitative.

On passing chlorine into a solution of 0·535 g. iodo-mesitylene for 30 minutes no deposit was observed. Evaporation of the solvent gave a yellowish oily precipitate which did not solidify. This was titrated against N/10 thiosulphate solution (made by diluting 10 c.c. N thiosulphate solution to 100 c.c.) and required 14·5 c.c. for neutralisation of the iodine liberated.

$$\text{Therefore weight of dichloride} = \frac{0{\cdot}0317 \times 14{\cdot}5 \times 10}{20}$$

$$= 0{\cdot}2299 \text{ g. dichloride}$$

$$\text{But } 0{\cdot}535 \text{ g. iodo-mesitylene should give} \quad \frac{317 \times 0{\cdot}535}{246} \text{ g. dichloride}$$

$$= 0{\cdot}6896 \text{ g. dichloride}$$

$$\text{Therefore percentage dichloride} = \frac{0{\cdot}2299 \times 100}{0{\cdot}6896}$$

$$= 33{\cdot}3\%.$$

2-Iodo-3:5-dibromotoluene.

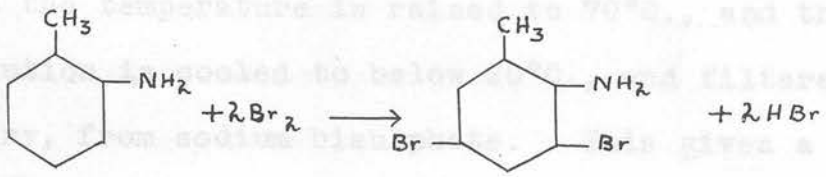
(a) 3:5-Dibromo-o-toluidine.

(McCrae, J.C.S., 1898, 73, 690)

21·4 g. o-toluidine in 100 c.c. glacial acetic acid

22 c.c. bromine in 50 c.c. glacial acetic acid

Bromine (22 c.c.) in glacial acetic acid (50 c.c.) was stirred into o-toluidine (21·4 g.) dissolved in glacial acetic acid (100 c.c.). The paste so obtained was poured into water, filtered, well washed with water and dried on a porous plate. It was dissolved in hot, dilute alcohol, refluxed with animal charcoal and filtered hot. On cooling, 51 g. (95%) of colourless crystals were obtained, of m.p. 50°.



(b) 2-Iodo-3:5-dibromotoluene.

McCrae (loc. cit.) carried out the diazotisation of the dibromo-o-toluidine, using concentrated sulphuric acid, pouring the diazo solution into hot potassium iodide solution, and removing iodine with sulphur dioxide. A better method, however, is that

described by Hodgson and Walker (J.C.S., 1933, 1620) for weakly basic naphthalene bases, and here extended to benzene derivatives. As the method has been used extensively in the present work the general procedure is detailed below:-

The amine is dissolved in hot glacial acetic acid and the solution cooled rapidly to room temperature. (In general, 1 g. amine to 12 c.c. acetic is recommended, but in some cases more or less solvent can be used, depending upon the solubility of the amine). By this means the amine is obtained in a finely crystalline state suitable for diazotisation.

Meanwhile the requisite amount of sodium nitrite is well powdered and added in portions, with vigorous stirring, to concentrated sulphuric acid (7 c.c. to 1 g. nitrite), cooled to below 20°C. by surrounding with water. In order to dissolve all the nitrite the temperature is raised to 70°C., and then the solution is cooled to below 20°C., and filtered, if necessary, from sodium bisulphate. This gives a solution of nitrosyl sulphuric acid.

Then the amine solution is added gradually, with stirring, to this nitrite-acid mixture, the temperature being kept below 20°C., and after filtration the solution is ready for treatment with potassium iodide. The method is remarkably successful, especially with naphthalene derivatives, yields in the region of 85% being claimed by Hodgson and Walker.

Also it avoids the use of a large excess of sodium nitrite often necessary in such cases. A 10% excess of nitrite is recommended.

2 Iodo-3:5-dibromotoluene.

26·5 g. 3:5-dibromo-o-toluidine in 100 c.c glacial acetic acid

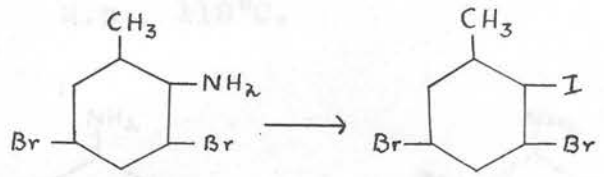
7·5 g. sodium nitrite in 52·5 c.c. conc. sulphuric acid

20 g. potassium iodide in 100 c.c. water

Dibromo-o-toluidine (26·5 g.) was dissolved in cold glacial acetic acid (100 c.c.) and added to a solution of sodium nitrite (7·5 g.) in concentrated sulphuric acid (52·5 c.c.) with vigorous stirring and cooling. The latter solution became dark, and after 30 minutes' continued stirring, the mixture was poured into the solution of potassium iodide (20 g. in 100 c.c. water). Effervescence took place. When the solution had been stirred for half-an-hour it was heated on the steam-bath for forty minutes. A heavy black oil separated. Sodium bisulphite was added to destroy free iodine, the supernatant liquid was decanted, and the oil was distilled in steam. A heavy brown oil passed over and solidified in the receiving beaker. The solid was filtered and dried, dissolved in hot glacial acetic acid and the solution was refluxed with

a few grams of animal charcoal and filtered hot. On cooling, the solution deposited long colourless needles of m.p. 68°C. (as quoted by McCrae, loc. cit.).

Yield, 22 g. (60%).



Dichloride (McCrae, loc. cit.)

Quantitative.

0·0424 g. precipitate required 18·25 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0447 \times 18{\cdot}25 \times 100}{20 \times 0{\cdot}0424}$$

$$= 96\%.$$

2:4:6-Tribromo-iodobenzene.

(a) 2:4:6 Tribromaniline.

(Sudborough and James, "Practical Organic Chemistry", p. 113)

93 g. aniline in 320 c.c. glacial acetic acid

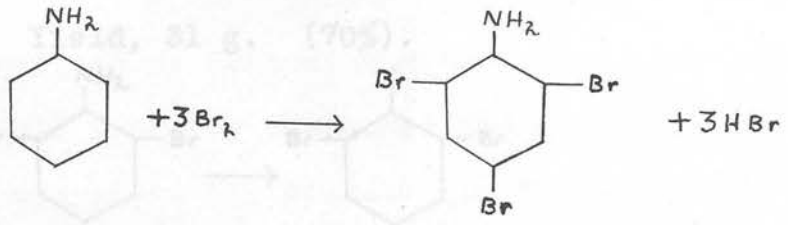
176 c.c. bromine in 350 c.c. glacial acetic acid.

The bromine solution was added to the aniline solution contained in a 2-litre beaker, and well stirred. Hydrogen bromide was copiously evolved and a yellow paste formed which was stirred for one

hour and then poured into water. The white precipitate thus obtained was filtered, washed with water and dried.

Yield, theoretical.

M.p., 118°C.



(b) 2:4:6-Tribromo-iodobenzene.

Hodgson and Walker's method (p. 64) was preferred to that of McCrae (loc. cit.)

33 g. tribromaniline in 400 c.c. glacial acetic acid.

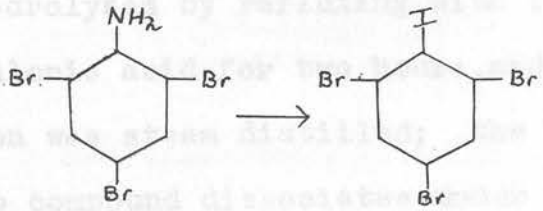
7·6 g. sodium nitrite in 55 c.c. conc. sulphuric acid.

20 g. potassium iodide in 100 c.c. water.

Tribromaniline (33 g.) was dissolved in hot glacial acetic acid (400 c.c.) and obtained in finely crystalline state by cooling to room temperature. This mixture was added to the solution of sodium nitrite (7·6 g.) in concentrated sulphuric acid (55 c.c.) cooled to below 20°C. This gave a clear brown solution which was stirred into the potassium iodide solution (20 g. in 100 c.c. water). Effervescence took place and a dark brown precipitate separated. A little

bisulphite was added and the mixture was heated for fifteen minutes on the steam-bath, then allowed to cool. The precipitate was filtered and washed, giving 37 g. of a clean solid. From alcohol it recrystallised in long colourless needles. The m.p., 105·5°C., agrees with that quoted by McCrae (loc. cit.)

Yield, 31 g. (70%).



Dichloride. (McCrae, loc. cit.).

Quantitative.

0·0605 g. precipitate required 17·3 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0512 \times 17{\cdot}3 \times 100}{20 \times 0{\cdot}0605}$$

$$= 73\%.$$

2-Iodo-3-nitrotoluene.

(a) 3-Nitro-o-toluidine.

(Reverdin and Crépieux, Ber., 1900, 33, 2498).

100 g. aceto-o-toluidide

262·5 g. fuming nitric acid in 87·5 g. glacial acetic acid.

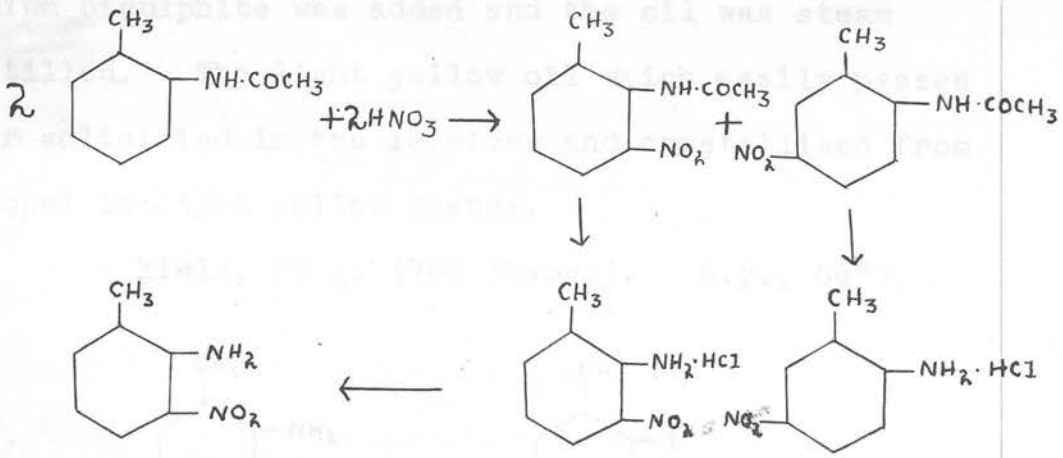
Aceto-o-toluidide (100 g.) was added in small portions, with stirring, to the 3:1 mixture of fuming nitric acid and glacial acetic acid (262·5 g. nitric and 87·5 g. acetic acid), the temperature being kept

below 7-8°C. by surrounding the containing flask with ice. The flask was then left for 12 hours at room temperature and the mixture was poured into water, giving a bright yellow precipitate consisting of a mixture of 3- and 5-nitro aceto-o-toluidides. This was filtered, washed with water, and dried. The crude nitro products were hydrolysed by refluxing with 3 parts concentrated hydrochloric acid for two hours, and then the acid solution was steam distilled; the hydrochloride of the 3-nitro compound dissociates under these conditions, the free base distilling over in the steam, whilst that of the 5-nitro compound remains behind in the flask.

The free 3-nitro-o-toluidine solidified in the receiver and was filtered, dried and recrystallised from alcohol.

Yield, 20 g. M.p., 96°C.

(The free 5-nitro-o-toluidine may be obtained by treating the acid solution left from the distillation with alkali, filtering, washing and recrystallising from alcohol).



(b) 2-Iodo-3-nitrotoluene.

(Wheeler and Liddle, Am. Chem. Jour., 1909, 42, 451).

20 g. 3-nitro-o-toluidine.

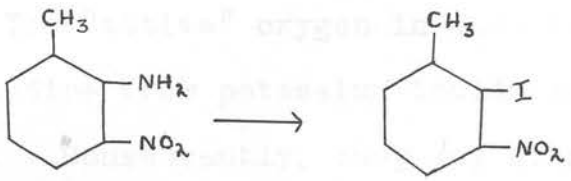
45 c.c. conc. sulphuric acid

13·5 g. powdered sodium nitrite.

95 g. potassium iodide in 180 c.c. water.

3-Nitro-o-toluidine (20 g.) was dissolved in concentrated sulphuric acid (45 c.c.) at 0°C. and sodium nitrite (13·5 g.) was added slowly with stirring. The mixture was allowed to stand at 0°C. for four hours and then was poured on to ice. An orange-red precipitate formed but dissolved almost immediately, leaving a pale yellow solution. Potassium iodide (95 g.) in water (180 c.c.) was added, with stirring, and a red precipitate appeared. This was decomposed by warming on the steam-bath, nitrogen being evolved with the separation of a heavy black oil. A little sodium bisulphite was added and the oil was steam distilled. The light yellow oil which easily passed over solidified in the receiver and crystallised from alcohol in light yellow plates.

Yield, 35 g. (70% theory). M.p., 66°C.

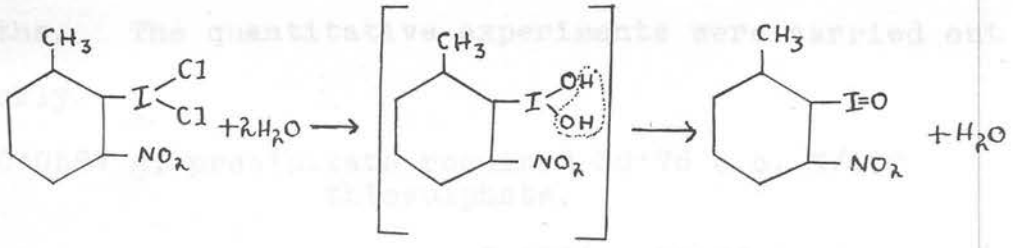


Dichloride.

The dichloride of 2-iodo-3-nitrotoluene is not described in the literature. It was here only isolated in small yield after several attempts.

The first attempts consisted in dissolving varying amounts (1·5 - 3 g.) of the compound in 30 c.c. chloroform, cooling and saturating with chlorine. On no occasion, however, was a deposit of the dichloride observed, even on leaving the flask corked for several days. Then on slowly drawing off the solvent in a vacuum desiccator, the original compound was invariably obtained, as proved by melting-point and mixed melting-point with the original compound.

But when the chloroform-chlorine solution was refluxed with sodium hydroxide solution and the chloroform was evaporated off, a yellowish precipitate was obtained. On filtration and washing with a small quantity of ether this gave a white amorphous powder, of m.p. 205 - 209°C. (with decomposition). This proved on analysis to be 2-iodoso-3-nitrotoluene, formed according to the equation:-



Analysis. The "active" oxygen in iodoso-compounds displaces iodine from potassium iodide (cf. the iodo-chlorides). Consequently, they may be analysed for

oxygen by using thiosulphate solution in a manner similar to that used for chlorine in the iodo-chlorides.

Found: "active" oxygen, 5·7%.

$C_7H_6(NO_2)IO$ requires 5·7%.

The formation of the iodoso-compound showed that some iodo-chloride was formed. Finally, by using 1·5 g. 2-iodo-3-nitrotoluene in 20 c.c. carbon tetrachloride, a small yield, 0·2 g., of the dichloride was obtained, in small yellow needles.

M.p., 75 - 76°C. with decomposition.

Analysis:

Found: "active" chlorine, 21·1%.

$C_7H_6(NO_2)ICl_2$ requires 21·2%.

Quantitative.

These results show that the dichloride is formed to quite a large extent, and the difficulty experienced in its isolation must be attributed to its extreme solubility in chloroform. It is also probable that the difficulty may be due to the instability of the dichloride, but a specimen kept in a corked tube only lost chlorine slowly over a period of several months. The quantitative experiments were carried out quickly.

0·0587 g. precipitate required 30·76 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0334 \times 30{\cdot}76 \times 100}{0{\cdot}0587 \times 20}$$

$$= 87{\cdot}5\%.$$

4:6-Dibromo-2-nitro-iodobenzene.

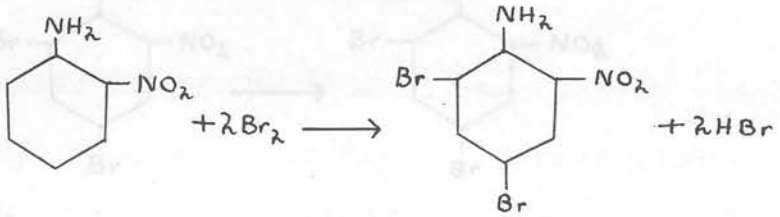
(a) 4:6-Dibromo-2-nitraniline.

(Jackson and Russe, Am. Chem. Jour., 1906, 35, 149).

20 g. o-Nitraniline in 200 g. glacial acetic acid

46·5 g. (15·5 c.c.) bromine in 30 c.c. glacial acetic acid.

Bromine (15·5 c.c.), dissolved in glacial acetic acid (30 c.c.), was added, with stirring, to a solution of o-nitraniline (20 g.) in glacial acetic acid (30 c.c.), the reaction mixture being cooled by surrounding with water. The mixture was poured into water and the yellow precipitate was filtered, washed with water and dried. On recrystallisation from dilute alcohol, 39 g. (90%) of yellow needles, m.p. 127°C., were obtained.



(b) 4:6-Dibromo-2-nitro-iodobenzene.

The preparation of this compound is not recorded in the literature. As the dibromo-nitraniline is weakly basic Witt's method of diazotisation was employed (see p. 77).

20 g. 4:6-dibromo-o-nitraniline

19 g. potassium metabisulphite

68 g. fuming nitric acid

26 g. iodine

50 g. potassium iodide.

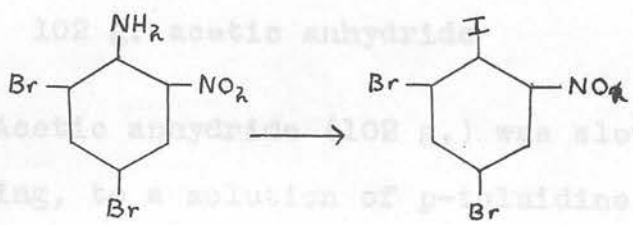
In this case a dark-coloured iodo-compound was obtained which, after filtration, was washed thrice with potassium iodide solution and water to remove iodine. One recrystallisation from alcohol gave m.p. 74-78°C., which rose to 79 - 81°C. on a further recrystallisation. Another recrystallisation brought this up to 81°C. (sharp) .

The yield of pale buff-coloured needles was 18 g. (63%).

Analysis (Micro-Dumas).

Found: N_2 , 3·3%.

$C_6H_2Br_2IN$ requires N_2 , 3·4%.



Dichloride.

After several unsuccessful attempts, the dichloride was obtained in very small yield by passing chlorine into 1· 5 g. of the compound dissolved in 25 c.c. chloroform at 0°C. The small lemon-yellow crystals obtained were filtered, washed with a little chloroform and dried on porous tile. The weight,

0·055 g., corresponds to only 3% of theory.

M.p., 86 - 88°C. (with decomposition).

Analysis.

Found: "active chlorine", 14·6%.

$C_6H_2Br_2(NO_2)ICl_2$ requires 14·8%.

Quantitative.

0·0610 g. precipitate required only 1·10 c.c. N/100 thiosulphate..

$$\text{Percentage dichloride} = \frac{0{\cdot}0478 \times 1{\cdot}10 \times 100}{20 \times 0{\cdot}0610}$$

$$= 4{\cdot}3\%.$$

4-Iodo-3:5-dinitrotoluene.

(a) Aceto-p-toluidide.

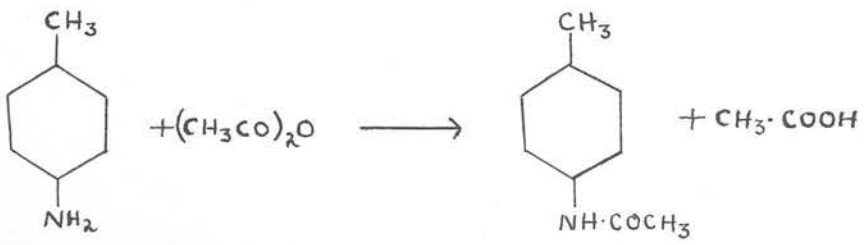
(Kaufmann, Ber., 1909, 3480).

107 g. p-toluidine

200 c.c. dry benzene

102 g. acetic anhydride

Acetic anhydride (102 g.) was slowly added, with shaking, to a solution of p-toluidine (107 g.) in dry benzene (200 c.c.). After standing overnight, the product was filtered, washed with benzene, and dried. An almost quantitative yield of shining plates was obtained. M.p., 155°C.



(b) 4-Amino-3:5-dinitrotoluene.

(Jackson and Ittner, Amer. Chem. Jour., 1897, 5)

100 g. aceto-p-toluidide

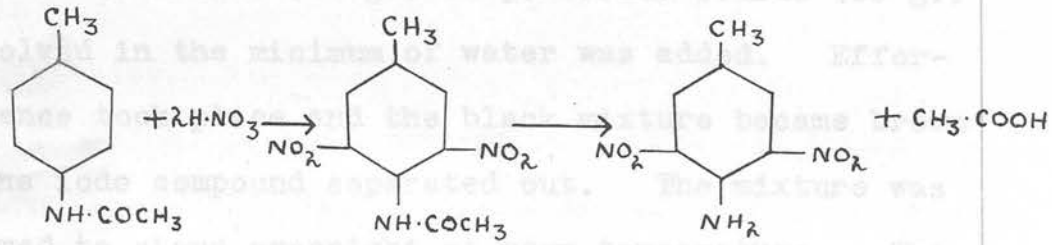
400 g. nitric acid (S.G. 1·44)

Aceto-p-toluidide (100 g.) was added in small quantities to the well-stirred nitric acid (400 g., S.G., 1·44) at 0°C. After complete addition, the stirring was continued for one hour and then the mixture was poured on to ice; the dinitro-toluidide separated as a copious brown precipitate which was filtered, washed with water and dried.

Yield: 90 g. M.p., 191°C.

The dinitrotoluidide (90 g.) was hydrolysed by boiling with sulphuric acid (600 c.c. ; S.G. 1·44) for 15 minutes. The product was cooled, filtered, dried and recrystallised from alcohol.

Yield, 65 g. M.p., 167·5°C.



(c) 4-Iodo-3:5-dinitrotoluene.

(W. S. Haldane, Thesis, Edinburgh 1934).

The 4-amino-3:5-dinitrotoluene was converted to the corresponding iodo compound, using Witts' method of diazotisation for weakly basic amines. The method

is here described in detail.

20 g. 4-amino-3:5-dinitrotoluene

12·5 g. potassium metabisulphite ($K_2S_2O_5$)

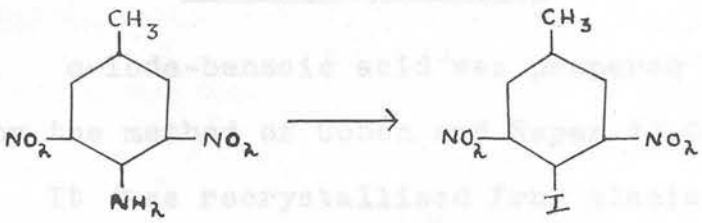
45 c.c. fuming nitric acid

17 g. iodine

33 g. potassium iodide

4-Amino-3:5-dinitrotoluene (20 g.) and potassium metabisulphite (12·5 g.) were finely powdered in a mortar to give a fine mixture. This was gradually added in very small amounts to fuming nitric acid (45 c.c.) contained in a beaker, and cooled to 0°C. The mixture was stirred with a thermometer after each addition, and temperature noted. (The temperature must be kept below 10°C.; otherwise the reaction may become explosive). After complete addition, the mixture was poured on to crushed ice (220 g.), and as quickly as possible a solution of iodine (17 g.) in potassium iodide (33 g.) dissolved in the minimum of water was added. Effervescence took place and the black mixture became brown as the iodo compound separated out. The mixture was allowed to stand overnight at room temperature. The iodo-compound was filtered and washed alternately with potassium iodide solution and water till the colour of iodine disappeared from the filtrate. Recrystallisation from alcohol gave yellowish-brown crystals, m.p., 157·5 - 158°C.

Yield: 20 g. (66% theory).



Dichloride.

This dichloride has not been described in the literature. It could not be isolated during the the course of the present work, even after repeated efforts in which the quantity of starting material and solvent was varied. On evaporation of the solvent the original substance, as proved by melting point and mixed melting-point, was always obtained. Boiling with sodium hydroxide solution, in order to ascertain whether any iodoso-derivative had been formed, also proved fruitless. In all cases the original was regained. That no dichloride is formed with 4-iodo-3:5-dinitrotoluene was proved by quantitative experiments.

Quantitative.

1 g. of the compound was dissolved in 20 c.c. chloroform at 0°C. and chlorine passed in for thirty minutes. No deposit was observed. On evaporation of the solvent, a precipitate was obtained which liberated no iodine from thiosulphate solution. In this case, therefore, there is apparently total prevention of the formation of the iodo-chloride.

o-Iodo-benzoic acid.

o-Iodo-benzoic acid was prepared in 85% yield by the method of Cohen and Raper (J.C.S., 1904, 1272). It was recrystallised from glacial acetic acid to which some water had been added, giving m.p. 161°C.

Dichloride. (Adkenasy and Meyer, Ber., 1893, 26, 1358).

Quantitative.

0·0375 g. precipitate required 22·85 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0319 \times 22{\cdot}85 \times 100}{20 \times 0{\cdot}0375}$$

$$= 97\%.$$

2:5-Diiodo-toluene.

(a) 5-Iodo-o-toluidine.

(Wheeler and Liddle, Am. Chem. Jour., 1909, 42, 501).

21·4 g. o-toluidine

50·8 g. iodine

20 g. powdered calcium carbonate

Iodine (50·8 g.) was dissolved in o-toluidine (21·4 g.) by shaking. Heat was evolved, substitution taking place and half of the base being converted to the

hydriodide according to the equation:-

$$2CH_3 \cdot C_6H_4 \cdot NH_2 + I_2 \longrightarrow I(CH_3)C_6H_3 \cdot NH_2 + CH_3 \cdot C_6H_4 \cdot NH_2 \cdot HI$$

The reaction was completed by adding powdered calcium carbonate (20 g.) and refluxing the mixture with an equal volume of water and two volumes of ether until the iodine colour has disappeared. The ether was then boiled off and the mixture steam distilled, the oil coming over in the distillate quickly solidifying in the receiver. This solid was filtered, dried and recrystallised from ligroin in colourless prisms of m.p. 90 - 91°C. The yield was 25 g. (54% theory).

$$2CH_3 \cdot C_6H_4 \cdot NH_2 + 2I_2 + CaCO_3 \longrightarrow 2I(CH_3)C_6H_3 \cdot NH_2 + CaI_2 + CO_2 + H_2O.$$

(b) 2:5-Diiodo-toluene.

(Wheeler and Liddle, loc. cit.)

9·5 g. 5-Iodo-o-toluidine

50 c.c. conc. hydrochloric acid in 150 c.c. water

4 g. sodium nitrite in 20 c.c. water

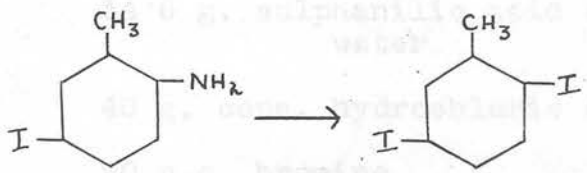
19 g. potassium iodide in 75 c.c. water.

5-Iodo-o-toluidine (9·5 g.) was mixed with concentrated hydrochloric acid (50 c.c.) and water (150 c.c.), well stirred and cooled to 0°C. Then a solution of sodium nitrite (4 g.) in water (20 c.c.) was slowly added and the mixture stirred for half-an-hour.

The solution was filtered from unconverted base (1 g.) and stirred into a solution of potassium iodide (19 g.) in water (75 c.c.). This gave a bulky precipitate which was allowed to stand for one hour at room temperature and then heated on the steam-bath for a similar period. Nitrogen was evolved and a black oil separated; excess iodine was neutralised with sodium bisulphite, the oil was extracted with ether and steam distilled. The solid thus obtained was filtered, washed with dilute alkali to remove any cresol formed, and then with a little ether. It was dried by pressing on filter paper and was recrystallised from alcohol.

M.p. (small yellow plates), 30 - 31°C.

Yield, 7·5 g. (64%).



2:5-Diiodo-toluene (0·5 g.) was dissolved in 8 c.c. chloroform, cooled to 0°C. and chlorine was passed in. At the end of only two minutes a yellowish precipitate separated which was filtered and washed with a little chloroform. Weight, 0·65 g.

Analysis of this precipitate by the usual method showed that it contained 25·2% of "active" chlorine. The dichloride, $C_7H_6I_2Cl_2$, requires 17·1%, whilst the tetrachloride, $C_7H_6I_2Cl_4$, requires 29·2%. Therefore, even when the solution was not fully saturated with chlorine, the two iodine atoms in

2:5-diiodotoluene exhibited no appreciable difference towards chlorine.

1:4-Diiodo-2:6-dibromobenzene.

(a) 2:6-Dibromo-sulphanilic acid.

Under ordinary conditions of bromination with bromine or bromine water, sulphanilic acid gives an almost quantitative yield of sym-tribromaniline, the sulphonic group being replaced by bromine. However, when sodium hypobromite solution is used as brominating agent this replacement of the sulphonic group only occurs to a very small extent. (Heinichen, Ann., 1889, 253, 269).

34·6 g. sulphanilic acid in 1 litre water

40 g. conc. hydrochloric acid

20 c.c. bromine

32 g. sodium hydroxide in 300 c.c. water.

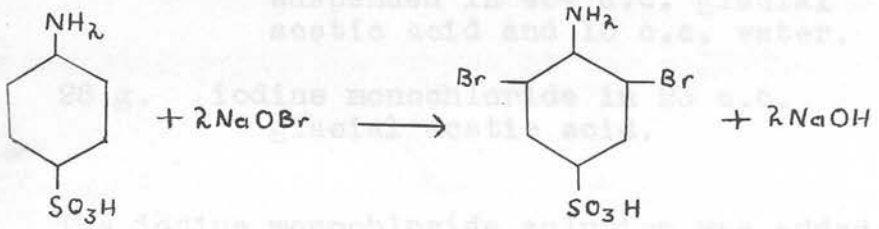
The sodium hypobromite solution was prepared by dissolving sodium hydroxide (32 g.) in water (300 c.c.) and adding bromine (32 c.c.). On stirring, a brownish solution was obtained. Meanwhile sulphanilic acid (34·6 g.) was dissolved in 1 litre of hot water with the addition of concentrated hydrochloric acid (40 g.). This solution was cooled to about 40°C., and the hypobromite solution was added from a separating funnel, with stirring. A brown colouration developed, and

after addition of hypobromite, the solution was filtered from a small amount of tribromaniline.

The barium salt of the dibromo-sulphanilic acid was isolated by the method of Orton and Pearson (J.C.S., 1908, 93, 735). The solution was neutralised with barium chloride and barium hydroxide solutions when the barium salt separated; weight, 76 g.

To obtain the free acid the barium salt was dissolved in hot water and the required amount of concentrated sulphuric acid was added carefully to precipitate the barium as barium sulphate. The hot solution was filtered from barium sulphate and allowed to cool. On acidification, the dibromo-sulphanilic acid separated out, further quantities being obtained by concentration of the solution. The acid is very soluble in water.

Yield, 56 g. of white crystalline solid (85%).



(b) 2:6-Dibromo-4-iodo-aniline.

This compound was prepared by Sudborough and Lakhumalumi (J.C.S., 1917, 111, 46) by the action of a glacial acetic acid solution of iodine monochloride (ICl) on dibromo-sulphanilic acid. Their experiment,

on a 0·5 g. scale, gave an 85% yield of the iodo-compound in which the sulphonic group had been replaced by iodine. This yield was here obtained on a much larger scale. The best preparation of iodine monochloride for this experiment is that given by Chattaway and Constable (J.C.S., 1914, 105, 124):-

Iodine (18·95 g.) was suspended in glacial acetic acid (23 c.c.) and chlorine was passed into the suspension which was vigorously shaken. All the iodine gradually went into solution and chlorine was passed in until orange crystals of iodine trichloride began to appear. Then the mixture was shaken with sufficient powdered iodine to react with the small quantity of iodine trichloride formed. When this had disappeared the acetic acid solution was ready for use. By this means about 28 g. of iodine monochloride were obtained.

$$I_2 + Cl_2 \longrightarrow 2ICl$$

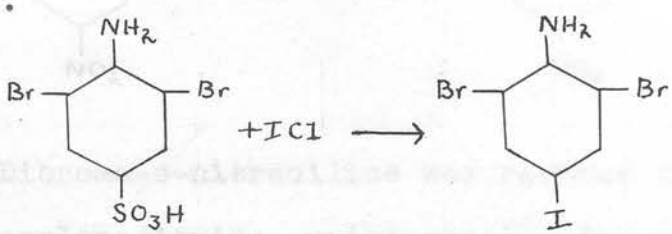
33·1 g. 2:6-dibromo-sulphanilic acid suspended in 40⁰ c.c. glacial acetic acid and 10 c.c. water.

28 g. iodine monochloride in 23 c.c. glacial acetic acid.

The iodine monochloride solution was added to the suspension of dibromo-sulphanilic acid and the mixture heated for two hours under reflux on a water-bath. About 3 g. unchanged acid were filtered off and the solution was allowed to cool thoroughly, when 11·4 g. of shining plates were obtained. These were filtered off and the solution was concentrated, giving

a further 18·6 g. of reddish-brown powder. Washing with potassium iodide solution partly removed this iodine colouration. Total yield, 29 g. (77%).

By recrystallising from glacial acetic acid solution the compound was obtained in long pink needles, m.p. 145 - 147°C. (Sudborough, loc. cit., quotes 147 - 148°C.).



Dichloride.

The dichloride of 2:6-dibromo-4-iodo-aniline was easily obtained from chloroform solution. It was formed almost instantaneously in the form of small red needles. The red colour is interesting, as this was the only red dichloride obtained in the course of this research.

The compound darkens from 60 - 70°C., finally decomposing with evolution of gas at 118 - 120°C.

Analysis.

Found: "active"chlorine, 15·8%

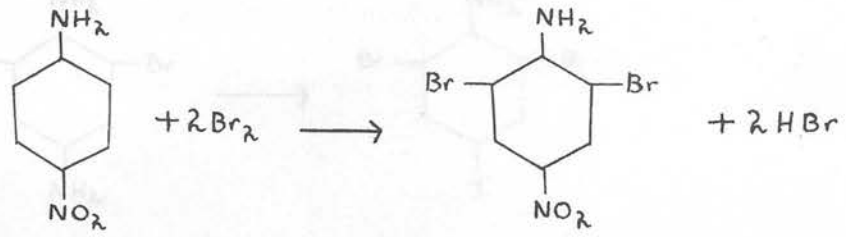
$C_6H_4NBr_2ICl_2$ requires 15·8%.

As a point of interest it was shown that 2:6-dibromo-4-iodo—aniline can be prepared from 2:6-dibromo-phenylenediamine by using conditions under which only one amino group is diazotised.

(1) 2:6-Dibromo-p-nitraniline was prepared from p-nitraniline.

(Claus and Willbaum, J. pr., 1897, 56, 61)

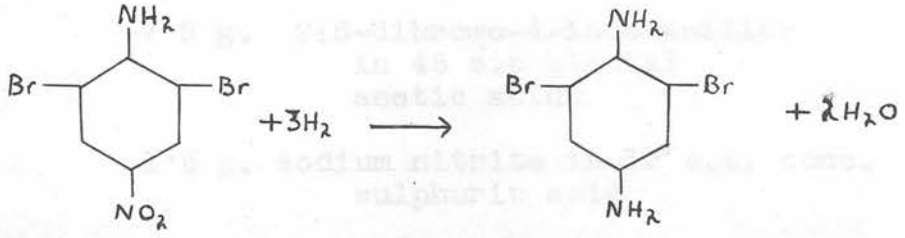
M.p., 200 - 202°C. (bright yellow needles).



(2) 2:6-Dibromo-o-nitraniline was reduced to 2:6-dibromo-p-phenylenediamine, using crystalline stannous chloride.

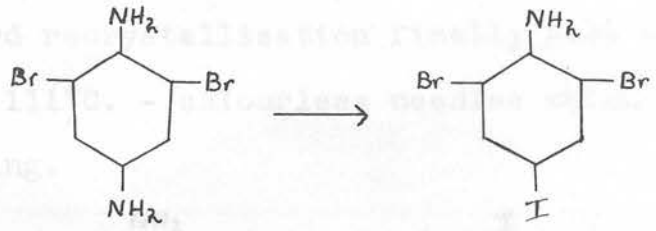
(Hewitt and Walker, J.C.S., 1907, 91, 1141)

M.p., 137°C. (colourless needles from water).



(3) Finally, 2:6-dibromo-p-phenylenediamine was dissolved in concentrated hydrochloric acid, diazotised with one molecular proportion of sodium nitrite, and treated with potassium iodide solution. The product was purified by recrystallisation from glacial acetic acid and melted at 145 - 147°C. In crystalline appearance it was similar to the compound obtained from the dibromo-sulphanilic acid. A mixed m.p. of the two compounds showed no change to that of the original substances. Finally, it gave a red

dichloride which darkened at 60°C. and decomposed at 120°C. A mixed m.p. of the two dichlorides showed a similar behaviour.



(c) 1:4-Diiodo-2:6-dibromobenzene.

The dibromo-iodoaniline was diazotised according to Hodgson and Walker's method (p. 64). The 1:4-diiodo-2:6-dibromobenzene obtained is not recorded in the literature.

7·5 g. 2:6-dibromo-4-iodo-aniline in 45 c.c glacial acetic acid.

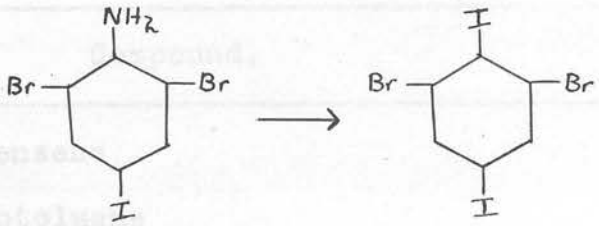
1·5 g. sodium nitrite in 12 c.c. conc. sulphuric acid

4 g. potassium iodide in 40 c.c. water.

The dibromo-iodoaniline was obtained in a finely crystalline state by dissolving in the hot glacial acetic acid and rapidly cooling to below 20°C. A clear brown diazo solution was obtained by adding the suspension of the base to the acid-nitrite mixture. On pouring the diazo solution into the potassium iodide solution effervescence took place and a brown precipitate appeared. After half-an-hour's stirring this was filtered and washed with potassium iodide solution and

water and dried. This gave 7·6 g. of a pinkish-coloured solid (77% theory).

One recrystallisation from alcohol gave m.p. 105 - 107°C., a second raised this to 108 - 110°C. and a third recrystallisation finally gave a m.p. of 110 - 111°C. - colourless needles which turned pink on standing.



Analysis. (Ter Meulen and Hessingla).

0·1068 g. gave 0·1843 g. mixed (AgI + AgBr)

0·1068 g. should give 0·1851 g. mixed (AgI + AgBr)

1:4-Diiodo-2:6-dibromobenzene (0·5 g.) was dissolved in 10 c.c. chloroform and chlorine was passed into the solution. At the end of five minutes the slightly yellow precipitate obtained was filtered, washed with chloroform and dried. Analysis showed it to contain 16·89% of "active" chlorine. The dichloride, $C_6H_2Br_2I_2Cl_2$, requires 12·7% and the tetrachloride, $C_6H_2Br_2I_2Cl_4$, requires 22·5%. Although it is impossible to state whether one iodine atom reacts more readily than the other, the figures show, at least, that both iodine atoms react with chlorine.

TABLE I.

Percentage Yields Of Iodo-Chlorides Obtained From Benzene Derivatives.

Compound.	Percentage.
Iodobenzene	100
o-Iodotoluene	96
m-Iodotoluene	91
p-Iodotoluene	90
o-Iodo-nitrobenzene	70
m-Iodo-nitrobenzene	98
p-Iodo-nitrobenzene	90
Iodo-mesitylene	33·3
3:5-Dibromo-2-iodotoluene	96
2:4:6-Tribromo-iodobenzene	73
2 Iodo-3-nitrotoluene	87·5
4:6-Dibromo-2-iodo-nitrobenzene	4·3
4-Iodo-3:5-dinitrotoluene	0
o-Iodo benzoic acid	97

NAPHTHALENE DERIVATIVES.

α-Iodonaphthalene.

It was found that this compound is more conveniently prepared by the diazotisation of α-naphthylamine hydrochloride than by the older method using concentrated sulphuric acid. (cf. Noelting, Ber., 1886, 19, 135).

(a) α-Naphthylamine hydrochloride.

40 g. α-naphthylamine in 200 c.c. hot alcohol

80 c.c. conc. hydrochloric acid.

The hydrochloric acid was added to the hot alcoholic solution of α-naphthylamine and the mixture was heated on the steam-bath until the salt began to separate. The solution was cooled and the mass of crystalline plates filtered off. Concentration of the solution gave a quantitative yield of the hydrochloride.

M.p., 286°C.

(b) α-Iodonaphthalene.

20 g. α-naphthylamine hydrochloride suspended in 170 c.c. water

20 c.c. conc. hydrochloric acid

8 g. sodium nitrite in 30 c.c. water

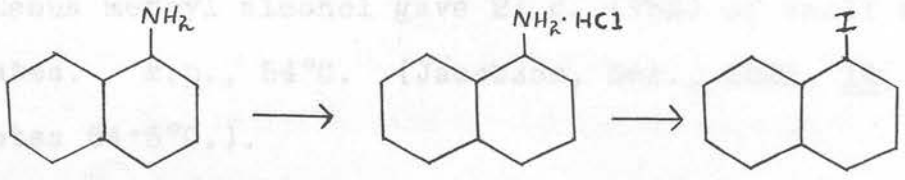
24 g. potassium iodide in 150 c.c. water.

The hydrochloric acid was added to the

suspension of the hydrochloride. This mixture was well stirred, cooled to 0°C., and diazotised with the sodium nitrite solution. Then the brown diazo solution was poured into the potassium iodide solution, when a brick-red colouration developed. After stirring for fifteen minutes the mixture was heated on the steam-bath for one hour. A heavy black oil separated which was extracted with ether, the ethereal solution being well washed with alkali. The ether was boiled off and the oil was steam distilled. It was again extracted with ether, dried over calcium chloride and the ether removed on the steam-bath. Finally it was distilled under reduced pressure. The oil thus obtained was practically colourless but darkened on standing.

Yield, 14 g. (50% - based on hydrochloride used)

B.p., 130°C./1·5 mm.



Dichloride (Willgerodt and Schlösser, Ber., 1900, 33, 692).

Quantitative.

1·123 g. α-Iodonaphthalene was used and the total precipitate was quickly titrated against N thiosulphate of which 8·80 c.c. were used.

$$\text{Weight of dichloride} = \frac{0{\cdot}0325 \times 8{\cdot}80 \times 100}{20}$$

$$= 1{\cdot}430 \text{ g.}$$

But 1·123 g. should give $\frac{325 \times 1{\cdot}123}{254}$

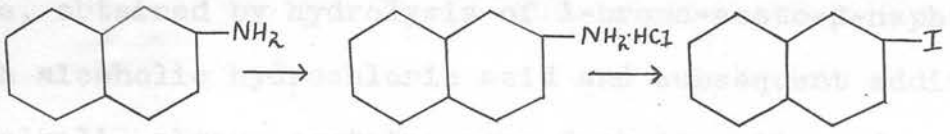
$= 1{\cdot}436$ g.

Therefore percentage dichloride $= \frac{1{\cdot}430 \times 100}{1{\cdot}436}$

$= 99{\cdot}6\%$

β-Iodonaphthalene.

β-Iodonaphthalene was prepared from β-naphthylamine hydrochloride (m.p. 260°C.) in a manner similar to that described for the α-isomer. In this case, however, the dark oil obtained solidified on cooling. The supernatant liquid was decanted and the solid was re-melted with hot water. Free iodine was removed with sodium bisulphite and then the compound was steam distilled. It solidified in pinkish plates in the receiver. Recrystallisation from aqueous methyl alcohol gave 21 g. (75%) of small white plates. M.p., 54°C. (Jacobson, Ber., 1881, 14, 804, quotes 54·5°C.).



Dichloride. (Willgerodt, Ber., 1894, 27, 592).

Quantitative.

1·376 g. β-iodonaphthalene was used and the total precipitate required 10·82 c.c. N thiosulphate.

Weight of dichloride $= \frac{0{\cdot}0325 \times 10{\cdot}82 \times 100}{20}$

$$= 1{\cdot}758 \text{ g.}$$

But 1·376 g. should give $\frac{325 \times 1{\cdot}376}{254}$

$$= 1{\cdot}761 \text{ g.}$$

Therefore percentage dichloride $= \frac{1{\cdot}758 \times 100}{1{\cdot}761}$

$$= 99{\cdot}9\%.$$

1-Bromo-β-iodonaphthalene.

Three methods were compared for the preparation of this compound:-

(1) Diazotisation of 1-bromo-β-naphthylamine, using concentrated sulphuric acid (Meldola, J.C.S., 1885, 47, 523).

(2) Diazotisation of 1-bromo-β-naphthylamine, using Hodgson and Walker's method.

(3) Diazotisation of 1-bromo-β-naphthylamine hydrochloride, using dilute hydrochloric acid.

The third method is to be recommended because isolation of the free base is unnecessary. The base, obtained by hydrolysis of 1-bromo-aceto-β-naphthalide with alcoholic hydrochloric acid and subsequent addition of alkali, always contains some dark impurity and requires several recrystallisations for purification.

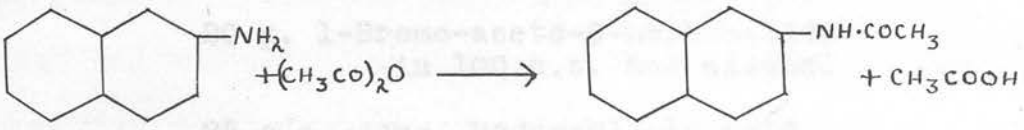
(a) Aceto-β-naphthalide.

(cf. Franzen and Eidis, J.pr., 1913, 88, 755).

100 g. β-naphthylamine in 200 c.c. hot benzene

68 c.c. acetic anhydride.

The acetic anhydride was added in small quantities to the hot benzene solution of β-naphthylamine. The naphthalide separated out on cooling. It was filtered and washed with benzene, giving 116 g. (90%) of pure white crystals of m.p. 133°C.



(b) 1-Bromo-aceto-β-naphthalide.

(Franzen and Eidis, loc. cit.)

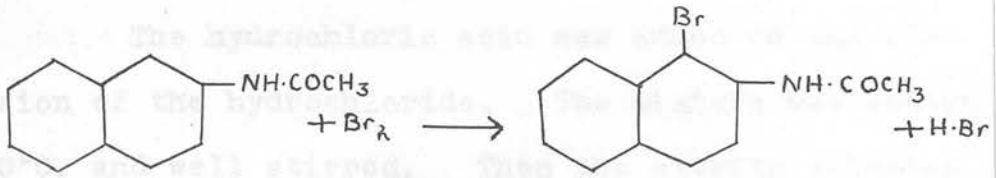
37 g. aceto-β-naphthalide in 200 c.c. chloroform

33 g. (11 c.c.) bromine in 40 c.c. chloroform.

The aceto-β-naphthalide was dissolved in the chloroform by warming on the steam-bath. Then the bromine solution was added to this warm solution with stirring. When about half the bromine had been added the bromo-naphthalide began to separate. After complete addition of bromine, the compound was filtered and washed with chloroform. It was then warmed with sodium carbonate solution to decompose any hydrobromide formed, filtered, washed with water and dried.

Yield, 52 g. (100%).

M.p., 139 - 140°C.



(c) 1-Bromo-β-naphthylamine hydrochloride.

(Franzèn and Eidis, loc. cit.)

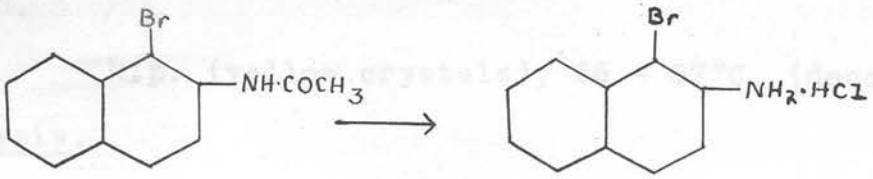
20 g. 1-Bromo-aceto-β-naphthalide
in 100 c.c. hot alcohol

25 c.c. conc. hydrochloric acid.

The bromo-aceto-β-naphthalide was dissolved in the hot alcohol, the hydrochloric acid was added and the mixture was refluxed for one hour. The alcohol was then removed on the steam-bath and the crystals of hydrochloride were filtered.

Yield, 19·5 g. (100%).

M.p., 219 - 220°C.(decomp.)



(d) 1-Bromo-β-iodonaphthalene.

10 g. 1-bromo-β-naphthylamine hydrochloride suspended in
70 c.c. water

10 c.c. conc. hydrochloric acid

3 g. sodium nitrite in 10 c.c. water

8 g. potassium iodide in 40 c.c. water.

The hydrochloric acid was added to the suspension of the hydrochloride. The mixture was cooled to 0°C. and well stirred. Then the nitrite solution was slowly added, giving a clear diazo solution. This was poured into the potassium iodide solution when effervescence took place. The mixture was heated on the steam-bath for one hour, sodium bisulphite was added and the solution allowed to cool. On cooling, a reddish precipitate separated which was filtered and washed with potassium iodide solution and water. From aqueous methyl alcohol 10 g. (75%) of stout red needles were obtained. The m.p., 94 - 95°C., agrees with that of Meldola (loc. cit.).

Dichloride.

This is not reported in the literature. It was easily obtained from chloroform solution in 60% yield.

M.p. (yellow crystals), 66 - 67°C. (decomp.).

Analysis.

Found: "active" chlorine, 17·5%.

$C_{10}H_6BrICl_2$ requires 17·6%.

Quantitative.

0·0410 g. precipitate required 18·1 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0404 \times 18{\cdot}1 \times 100}{0{\cdot}0401 \times 20} = 91{\cdot}2\%.$$

1:6-Dibromo-β-iodonaphthalene.

(a) Benzylidene-β-naphthylamine.

(Claisen, Ann., 1887, 237, 273)

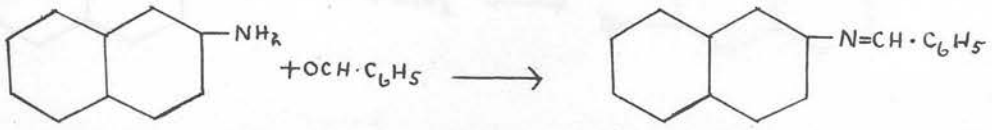
30 g. β-naphthylamine in 100 c.c. hot alcohol

23 g. freshly distilled benzaldehyde

The benzaldehyde was added to the alcoholic solution of β-naphthylamine and the mixture was refluxed for fifteen minutes, then allowed to cool. The yellow crystals of the benzylidene compound were filtered off, washed with alcohol and dried in air.

Yield, 45 g. (93%).

M.p., 102°C.



(b) 1:6-Dibromo-β-naphthylamine.

(Franzen and Eidis, J. pr., 1913, 88, 755)

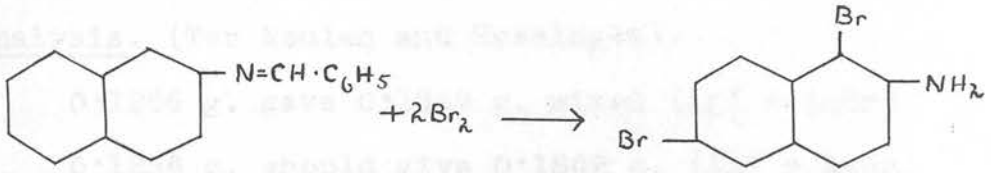
23·1 g. benzylidene-β-naphthylamine in 65 c.c. chloroform

32 g. bromine in 20 c.c. chloroform (2 equal portions)

The first portion of bromine was added to the benzylidene-β-naphthylamine solution with vigorous stirring at 15 - 25°C. The thick paste formed was

allowed to stand for two hours at room temperature, and pure pyridine (7·9 g.) was added when the solid dissolved. The second portion of bromine was added and the mixture, after standing for two hours, was refluxed with 25 c.c. alcohol for one hour. The hydrobromide of the base precipitated on cooling. This was filtered, washed with alcohol and dried. The free base was liberated by dissolving the solid salt in 150 c.c. alcohol with the addition of 20 c.c. concentrated ammonia and 10 c.c. water. On cooling, the base crystallised in long white needles, and by evaporation of the filtrate 26·8 g. was obtained altogether (75%).

M.p., 122 - 123°C.



(c) 1:6-Dibromo-β-iodonaphthalene.

This compound is not recorded in the literature. It was obtained here by diazotisation of 1:6-dibromo-β-naphthylamine according to Hodgson and Walker's method.

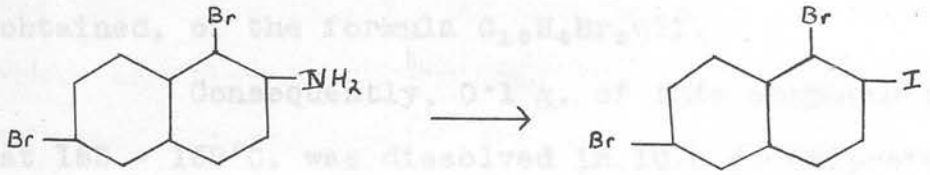
25 g. 1:6-dibromo-β-naphthylamine in 300 c.c. glacial acetic acid.

6·4 g. sodium nitrite in 45 c.c. conc. sulphuric acid.

20 g. potassium iodide in 100 c.c. water.

A clear diazo solution was obtained, similar to that obtained in the previous experiments, using this method. Treatment with the potassium iodide solution gave brisk effervescence, and after one hour the dark brown precipitate was filtered, washed with potassium iodide solution and water, and dried. Recrystallisation from acetic acid gave m.p. 106 - 110°C.; alcohol gave m.p. 110°C., and finally ethyl acetate gave small pink needles melting sharply at 111·5 - 112°C.

Yield, 20 g. (60%)



Analysis. (Ter Meulen and Hessingla).

0·1256 g. gave 0·1849 g. mixed (AgI + AgBr)

0·1256 g. should give 0·1862 g. (AgI + AgBr)

Dichloride.

This dichloride is not listed. It was obtained by passing chlorine into a chloroform solution of 1:6-dibromo-β-iodonaphthalene, 4 g. of which in 50 c.c. chloroform gave 3·9 g. (84%) dichloride. The chrome-yellow crystals melted at 67 - 68°C. (decomp.).

Analysis.

Found: "active" chlorine, 14·7%.

$C_{10}H_5Br_2ICl_2$ requires 14·7%.

The dichloride proved to be very unstable and decomposed on standing for twenty-four hours exposed

to the atmosphere. By this time the yellow colour had disappeared, leaving a dirty-white solid. This was dissolved in the minimum quantity of hot ethyl acetate and the solution was cooled rapidly to room temperature. A quantity of white plates separated. These were filtered and recrystallised again from ethyl acetate. The melting-point of 165 - 168°C. is far above that of the original dibromo-iodonaphthalene, and it was thought probable that as a decomposition product a nuclear chloro-substituted dibromo-iodonaphthalene had been obtained, of the formula $C_{10}H_4Br_2ClI$.

Consequently, 0·1 g. of this compound melting at 165 - 168°C. was dissolved in 10 c.c. chloroform, and chlorine was passed into the solution at 0°C. After one hour, a small quantity of minute yellow crystals separated. In a melting-point determination these darkened at 75 - 85°C. and decomposed finally at 90 - 95°C. Analysis gave 13·2% "active" chlorine. The fact that $C_{10}H_4Br_2ClICl_2$ requires 13·7% leads to the formulation of the decomposition product of 1:6-dibromo-β-iodonaphthalene dichloride as 1:6-dibromo-x-chloro-β-iodonaphthalene of m.p. 165 - 168°C.

Quantitative.

0·0242 g. precipitate required 10 c.c. N/100 thiosulphate

$$\text{Percentage dichloride} = \frac{0{\cdot}0483 \times 10 \times 100}{0{\cdot}0242 \times 20}$$

$$= 99{\cdot}8\%.$$

1-Nitro-β-iodonaphthalene.

(a) 1-Nitro-aceto-β-naphthalide.

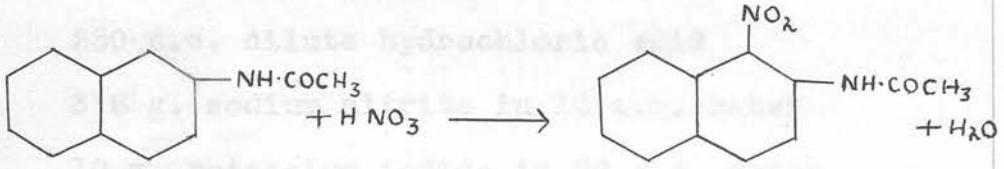
(Liebermann and Jacobson, Ann., 1882, 211, 44).

27 g. aceto-β-naphthalide suspended in 68 c.c. glacial acetic acid.

13·5 g. (9 c.c.) fuming nitric acid.

The nitric acid was slowly stirred into the suspension of the naphthalide. At first the naphthalide remained in suspension, but when about half the acid had been added it all went into solution. After complete addition of nitric acid the mixture was allowed to stand for two days. The yellow crystals which had appeared were filtered off (17 g.). Further quantities separated but these were neglected, as they consist of a mixture of other nitro-isomers.

The 1-nitro-aceto-β-naphthalide was recrystallised from alcohol in yellow needles, m.p., 123 - 124°C.



(b) 1-Nitro-β-naphthylamine.

17 g. 1-nitro-aceto-β-naphthalide in 200 c.c. hot alcohol

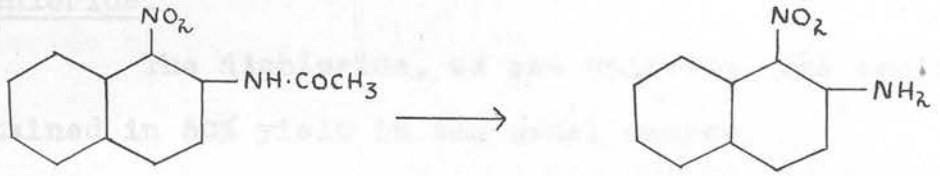
9 c.c. conc. hydrochloric acid.

The hydrochloric acid was added to the hot alcoholic solution, and the mixture was refluxed for

two hours. Most of the solvent was then boiled off and the solution was allowed to cool. Yellow crystals of 1-nitro-β-naphthylamine separated out.

Yield, 12·5 g. (90%).

The m.p. found was 128 - 129°C. Various melting-points ranging from 123 - 127°C. have been quoted. Sudborough and Beard (J.C.S., 1910, 97, 785) found that 1-nitro-β-naphthylamine gave a trinitrobenzene derivative of m.p. 115 - 116°C. The above specimen also gave this derivative with the same melting-point.



(c) 1-Nitro-β-iodonaphthalene.

(cf. Meldola, J.C.S., 1885, 47, 520).

10 g. 1-nitro-β-naphthylamine

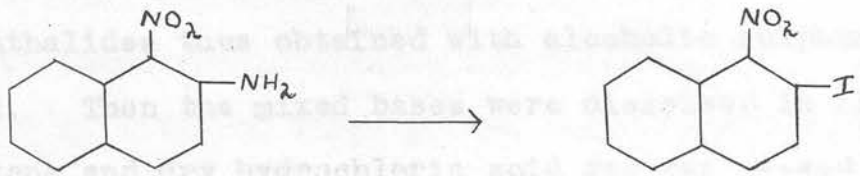
250 c.c. dilute hydrochloric acid

3·8 g. sodium nitrite in 10 c.c. water

10 g. potassium iodide in 20 c.c. water.

The nitro-base was suspended in the hydrochloric acid at 0°C., and the well-stirred solution was treated with the sodium nitrite, giving on filtering a clear diazo solution. This was poured into the potassium iodide solution. Effervescence took place. The mixture was heated on the steam-bath for half-an-hour.

On cooling, the crude iodo-compound was filtered, washed with potassium iodide solution and water, and dried. Red needles were obtained by recrystallisation from alcohol, m.p. 88·5°C. (Meldola quotes 88·5°C.). The yield, however, was disappointing - 7 g. (44%). Other methods of diazotisation are therefore to be advised.



Dichloride.

The dichloride, as yet unlisted, was easily obtained in 50% yield in the usual manner.

M.p. (golden yellow crystals), 68 - 72°C. (decomp.).

Analysis.

Found: "active" chlorine, 19·0%.

$C_{10}H_6NO_2ICl_2$ requires 19·2%.

Quantitative.

0·0416 g. precipitate required 11·75 N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0370 \times 11{\cdot}75 \times 100}{0{\cdot}0416 \times 20}$$

$$= 52\%.$$

2-Nitro-α-iodonaphthalene.

(a) 2-Nitro-α-naphthylamine.

2-Nitro-α-naphthylamine was obtained (along with 4-nitro-α-naphthylamine) by the method described by Hodgson and Walker (J.C.S., 1933, 1205). This consisted in nitrating aceto-α-naphthalide with nitric acid (d 1·42), and hydrolysing the mixed 2- and 4-nitronaphthalides thus obtained with alcoholic sulphuric acid. Then the mixed bases were dissolved in nitrobenzene and dry hydrochloric acid gas was passed in until fuming began. The 4-nitro-α-naphthylamine hydrochloride so formed was filtered off and dried. Treatment with water gave the free 4-nitro-α-naphthylamine, m.p. 193 - 194°C. (yellow needles from acetic acid). This isomer was obtained in about 65% yield.

The 2-nitro-α-naphthylamine was isolated from the filtrate as the sulphate. Then the free base was obtained by treatment of the sulphate with water (35% yield).

M.p., 143 - 144°C. (orange prisms from acetic acid).

(b) 2-Nitro-α-iodonaphthalene.

(cf. Meldola, J.C.S., 1885, 47, 519)

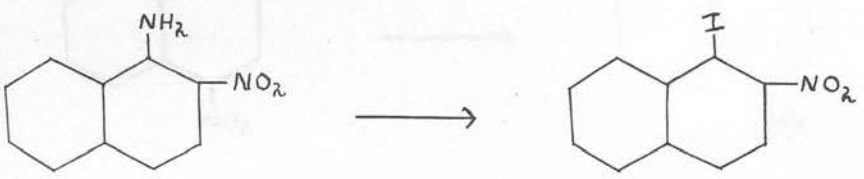
Hodgson and Walker's method of diazotisation was again used.

8·7 g. 2-nitro-α-naphthylamine in 105 c.c. glacial acetic acid

3·8 g. sodium nitrite in 30 c.c. conc. sulphuric acid

10 g. potassium iodide in 50 c.c. water.

The diazotisation followed the usual course, using this method. The dark precipitate obtained by treating the diazo solution with the potassium iodide solution was filtered, washed with potassium iodide solution and water, and dried. It was dissolved in hot alcohol, and animal charcoal was added. The solution was refluxed for 10 minutes and filtered hot. On cooling, 9 g. (65%) of large golden scales were obtained, of m.p. 108°C. (Meldola quotes 108·5°C.).



Dichloride.

The dichloride was obtained in 80% yield from chloroform.

M.p., 74°C. (decomp.).

Analysis.

Found: "active" chlorine, 19·2%.

$C_{10}H_6NO_2ICl_2$ requires 19·2%.

Quantitative.

0·0365 g. precipitate required 17·3 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0370 \times 17{\cdot}3 \times 100}{0{\cdot}0365 \times 20}$$

$$= 87{\cdot}7\%.$$

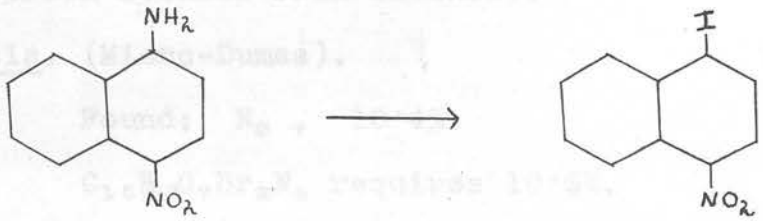
4-Nitro-α-iodonaphthalene.

(a) 4-Nitro-α-naphthylamine (see above).

(b) 4-Nitro-α-iodonaphthalene.

(cf. Meldola, loc. cit.).

The preparation was carried out exactly the same as that for the 2-nitro-isomer, using similar quantities. The compound in this case recrystallised from alcohol in golden needles, m.p. 123 - 124°C. (Meldola quotes 123°C.).



Dichloride.

The dichloride isolated from chloroform in bright yellow crystals darkens at 98°C. and decomposes at 104 - 108°C.

Analysis.

Found: "active" chlorine, 19·1%.

$C_{10}H_6NO_2ICl_2$ requires 19·2%.

Quantitative.

0·0297 g. precipitate required 14·4 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0370 \times 14{\cdot}4 \times 100}{0{\cdot}0297 \times 20}$$

$$= 89{\cdot}7\%.$$

2:4-Dibromo-α-iodonaphthalene.

(a) 2:4-Dibromo-α-naphthylamine.

(Franzen and Aasland, J. pr., 1917, 95, 165)

This compound was made from benzylidene-α-naphthylamine (m.p., 72°C.) in manner analogous to that already described for the preparation of 1:6-dibromo-β-naphthylamine.

M.p., 117°C. (needles from alcohol).

The base formed a picrate of m.p. 135°C. (dark brown needles from alcohol).

Analysis. (Micro-Dumas).

Found: N_2 , 10·4%.

$C_{16}H_{10}O_7Br_2N_4$ requires 10·6%.

(b) 2:4-Dibromo-α-iodonaphthalene.

This compound has not been yet described but was here obtained by diazotisation of the dibromo-base in a manner similar to that used for the 1:6-dibromo-β-iodo-compound.

6·5 g. 2:4-dibromo-α-naphthylamine in 78 c.c. glacial acetic acid.

2 g. sodium nitrite in 14 c.c. conc. sulphuric acid.

4 g. potassium iodide in 25 c.c. water.

In this case the crude compound was recrystallised (twice) from glacial acetic acid.

Yield, 4·2 g. (50%).

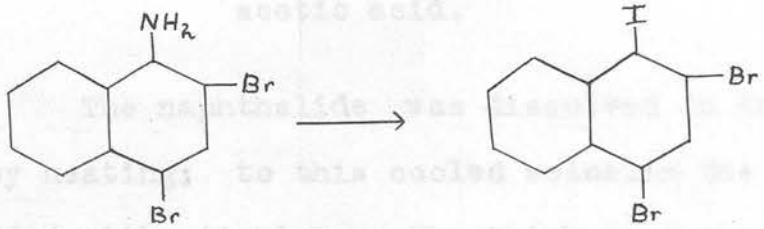
The compound, when pure, melts at 115-117°C.

This is remarkably close to the m.p. of the original, but a mixed melting-point determination gave a large depression. Also the iodo-compound forms no picrate.

Analysis. (Ter Meulen and Hessingla)

0·1349 g. gave 0·1885 g. mixed (AgI + AgBr)

0·1349 g. should give 0·2000 g. (AgI + AgBr).



Dichloride.

Proving that the iodo-compound had indeed been obtained, a dichloride was easily formed (65%).

M.p. (dark chrome plates), 78 - 83°C. (decomp.).

Analysis.

Found: "active" chlorine, 14·7%.

$C_{10}H_5Br_2ICl_2$ requires 14·7%.

The dichloride is quite stable and only decomposes slowly on standing.

Quantitative.

0·0229 g. precipitate required 8·15 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0483 \times 8{\cdot}15 \times 100}{0{\cdot}0229 \times 20}$$

$$= 86\%.$$

2-Nitro-4-bromo-α-iodonaphthalene.

(a) 4-Bromo-aceto-α-naphthalide.

(Meldola, Ber., 1878, 11, 1906)

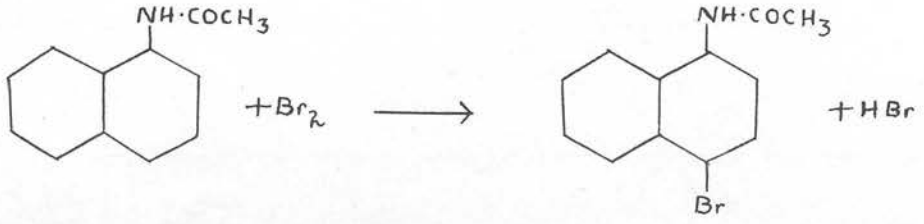
20 g. aceto-β-naphthalide in 100 c.c. glacial acetic acid.

6 c.c. bromine in 15 c.c. glacial acetic acid.

The naphthalide was dissolved in the acetic acid by heating; to this cooled solution the bromine was added with stirring. The thick paste obtained on pouring into water was filtered, dried and recrystallised from glacial acetic acid.

M.p., 193°C.

Yield, 26 g. (91%).



(b) 2-Nitro-4-bromo-aceto-α-naphthalide.

(Liebermann, Ann., 1876, 183, 260).

25 g. 4-bromo-aceto-β-naphthalide in 500 c.c. glacial acetic acid

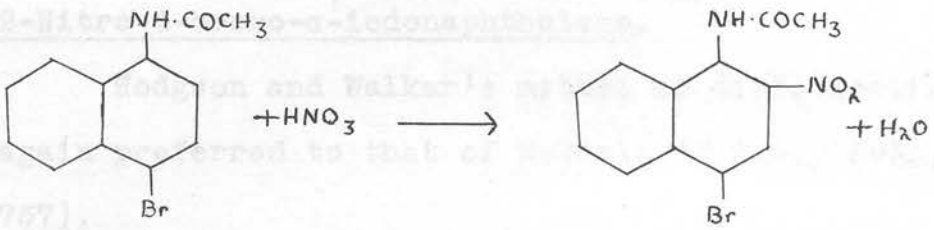
8·5 c.c. fuming nitric acid.

The nitric acid was added, with stirring, to the solution of the bromo-naphthalide maintained at a temperature of 60 - 70°C. The yellow nitro compound

separated out. When the mixture had cooled, the nitro-naphthalide was filtered, washed and recrystallised from glacial acetic acid. It was obtained in long yellow needles.

M.p., 230 - 232°C.

Y ield, 20 g. (70%).



(c) 2-Nitro-4-bromo-α-naphthylamine.

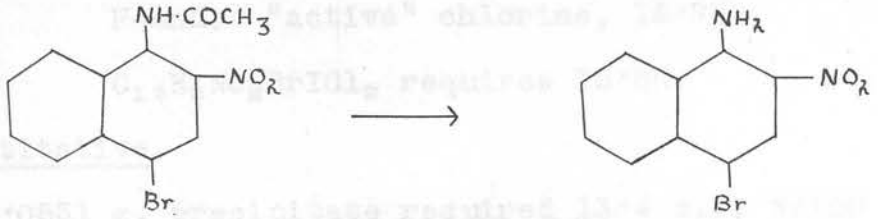
Hydrolysis of the naphthalide was first tried, using an alcoholic-hydrochloric acid mixture. Even after 12 hours' refluxing, however, the naphthalide was recovered unchanged.

The method of Meldola (J.C.S., 1885, 47, 500) proved effective.

20 g. of the naphthalide were dissolved in 150 c.c. concentrated sulphuric acid, and 30 c.c. water were slowly added. The solution became hot and was allowed to stand for fifteen minutes (no external heating is required). It was then poured into a large volume of water, when the red base precipitated. From alcohol it was obtained in dark red needles.

M.p., 199°C.

Y ield, 15 g. (87%).



(d) 2-Nitro-4-bromo-α-iodonaphthalene.

Hodgson and Walker's method of diazotisation was again preferred to that of Meldola (J.C.S., 1892, 61, 767).

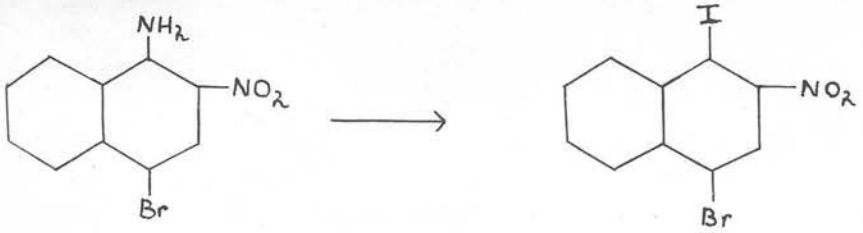
15 g. 2-nitro-4-bromo-α-naphthylamine in 400 c.c. glacial acetic acid.

4·2 g. sodium nitrite in 30 c.c. conc. sulphuric acid.

10 g. potassium iodide in 50 c.c. water.

The diazotisation followed the course of those already described. The crude iodo compound was recrystallised from glacial acetic acid. The pure compound forms small yellowish-brown needles, m.p. 117-118°C.

Yield, 12 g. (60%).



Dichloride

The dichloride was obtained in small yield from chloroform. It melts at 105 - 110°C. (decomp.).

Analysis.

Found: "active" chlorine, 15·7%.

$C_{10}H_5NO_2BrICl_2$ requires 15·8%.

Quantitative.

0·0531 g. precipitate required 13·4 c.c. N/100 thiosulphate.

$$\text{Percentage dichloride} = \frac{0{\cdot}0449 \times 13{\cdot}4 \times 100}{0{\cdot}0531 \times 20}$$

$$= 56{\cdot}7\%.$$

Finally the compound, 2:4-dinitro-α-iodonaphthalene, was prepared from 2:4-dinitro-α-naphthylamine. (For preparation of the latter see Morgan and Evans, J.C.S., 1919, 185, 1129).

But it was found that the dinitro-iodo compound is practically insoluble in chloroform and it was not studied further.

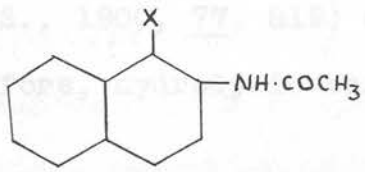
TABLE II.

Percentage Yields Of Iodo-Chlorides Obtained From Naphthalene Derivatives.

Compound.	Percentage.
α-Iodo-naphthalene	99·6
β-Iodo-naphthalene	99·9
1-Bromo-β-iodo-naphthalene	91·2
1:6-Dibromo-β-iodo-naphthalene	99·8
1-Nitro-β-iodo-naphthalene	52
2-Nitro-α-iodo-naphthalene	87·7
4-Nitro-α-iodo-naphthalene	89·7
4-Bromo-2-nitro-α-iodo-naphthalene	56·7
2:4-Dibromo-α-iodo-naphthalene	86

HYDROLYSIS OF SUBSTITUTED ACETYL NAPHTHYLAMINES.

Various substituted naphthylamines were prepared as intermediate products in the course of the research. The majority of these were obtained by the hydrolysis of the corresponding acetyl derivatives. In general, it was found that whereas α-substituted-aceto-β-naphthalides (I) were easily hydrolysed, using alcoholic hydrochloric acid, β-substituted-aceto-α-naphthalides (II) were resistant to this hydrolysing agent.



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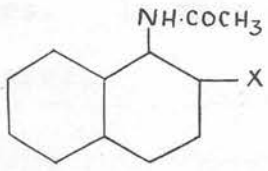


II

This line was therefore extended and a short qualitative comparison of the α- and β-naphthalides was carried out. The method consisted in dissolving 1 g. of the naphthalide in 10 c.c. hot alcohol, adding 0·5 c.c. hydrochloric acid and refluxing the mixture on the steam-bath. The results obtained are summarised briefly below. Reference is also given to the work previously described bearing on this examination.

α-Substituted-aceto-β-naphthalides.

1-Bromo-aceto-β-naphthalide.

(See also p. 94).

1 g. of the naphthalide was refluxed with 10 c.c. alcohol and 0·5 c.c. concentrated hydrochloric acid for one hour. The solution was allowed to cool and a little ammonia was added to neutralise the hydrochloric acid. White crystals separated, plus some dark impurity. These crystals were purified by recrystallisation from petrol ether (40 - 60), and gave m.p. 63 - 64°C. This agrees with the melting-point of 1-bromo-β-naphthylamine, 63 - 64°C., quoted by Meldola (J.C.S., 1900, 77, 819) and others. In this case, therefore, hydrolysis was successful.

1-Nitro-aceto-β-naphthalide (p. 100).

Similar quantities were used as in the above experiment. On adding ammonia and concentrating the solution somewhat, yellow crystals separated, m.p. 127-8°C. This agrees with the melting-point of 1-nitro-β-naphthylamine as already found. Again hydrolysis had been effected in one hour.

1:6-Dibromo-aceto-β-naphthalide.

1:6-Dibromo-aceto-β-naphthalide was obtained by the action of acetic anhydride on 1:6-dibromo-β-naphthylamine in benzene solution. It melts at 212°C.

(Lawson, Ber., 1885, 18, 2624).

Hydrolysis was easily effected by refluxing for one hour. The white crystals obtained melted at 122 - 123°C.

β-Substituted-aceto-α-naphthalides.

2:4-Dibromo-aceto-α-naphthalide.

2:4-Dibromo-aceto-α-naphthalide was obtained by acting on 2:4-dibromo-α-naphthylamine in benzene with acetic anhydride. The naphthalide melts at 225°C. (Meldola, Ber., 1878, 11, 1906).

In this case the naphthalide was recovered unchanged, m.p. 225°C. Also a further experiment was carried out using 8 g. of the naphthalide in 25 c.c. alcohol and 10 c.c. concentrated sulphuric acid. But even on refluxing this mixture for eight hours the unchanged naphthalide was recovered, m.p. 223°C.

2-Nitro-4-bromo-aceto-α-naphthalide.

As already described on p. 109, the hydrolysis of this compound was attempted unsuccessfully, using alcoholic-hydrochloric acid. Further attempts on the present small scale similarly proved fruitless. The naphthalide, m.p. 230 - 232°C., was recovered unchanged.

2:4-Dinitro-aceto-α-naphthalide.

2:4-Dinitro-aceto-α-naphthalide was prepared by the dinitration of aceto-α-naphthalide (Morgan and

Evans, J.C.S., 1919, 185, 1129). The yellow needles obtained from alcohol melted at 250°C.

Attempts to effect hydrolysis with alcoholic-hydrochloric acid were unsuccessful, the unchanged naphthalide being obtained in each case, m.p. 250°C.

SUBSTITUTED THIOBENZOIC ACIDS.

Thiobenzoic acid, C_6H_5COSH, was first prepared by Kym (Ber., 1899, 32, 3533) by the action of benzoyl chloride on an alcoholic solution of potassium hydrosulphide, KSH. Kym also prepared p-nitro-thiobenzoic acid, starting from p-nitro benzoyl chloride. This latter preparation was subsequently modified by Hansen and Fosdick (J.A.C.S., 1933, 55, 2872).

In the present work thiobenzoic acid was prepared by Kym's method and p-nitro-thiobenzoic was obtained, using the method of Hansen and Fosdick. The latter method was also adopted for the preparation of the hitherto unknown o-chloro- and o-bromo-thiobenzoic acids, both unstable liquids. To obtain 2:4:6-tribromo-thiobenzoic acid (also unknown) still further modifications of Kym's original method had to be employed.

Pawlewski (Ber., 1898, 31, 661) found that thioacetic acid, Ch_3COSH, reacted with amines to give acetyl compounds:-

$$R - NH_2 + HSOC - CH_3 \longrightarrow R - NH - OC \cdot CH_3 + H_2S$$

Similarly, Wheeler (J.A.C.S., 1901, 23, 445) obtained benzanilide from thiobenzoic acid and aniline:-

$$C_6H_5 - COSH + H_2NC_6H_5 \longrightarrow C_6H_5CONHC_6H_5 + H_2S.$$

Consequently, with the thiobenzoic acids isolated several condensations were carried out with amines. In order to prove the identity of the anilides

thus formed, the corresponding condensations with benzoyl chlorides were effected:-

$$R - COCl + H_2N - R' \longrightarrow R - CONH - R' + HCl.$$

Thus the anilides obtained by both methods were compared by melting-points and mixed melting-points. Where unknown, the anilides were analysed for nitrogen by the Micro-Dumas method.

Those compounds containing sulphur and which are not listed were analysed for sulphur by the method described in Cumming and Kay, "Quantitative Chemical Analyses", 1928, p. 287.

Thiobenzoic Acid.

(Kym, Ber., 1899, 32, 3533).

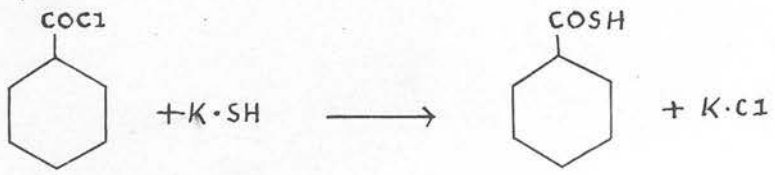
20 g. pure benzoyl chloride

20 g. potassium hydroxide dissolved in absolute alcohol.

The alcoholic potassium hydroxide solution was saturated with sulphuretted hydrogen (H_2S) until a greenish colour developed. This gave an alcoholic solution of potassium hydrosulphide, KSH. Then the benzoyl chloride was added gradually and the mixture was heated for a few minutes on the steam-bath. Insoluble potassium chloride was removed by filtration and the alcoholic filtrate was evaporated to dryness. This gave the yellow potassium salt of the acid. To obtain the free acid the salt was dissolved in water, insoluble matter was filtered off, and dilute sulphuric

acid was added. A brown oil separated which was extracted with ether, the ethereal solution being dried over calcium chloride. The ether was drawn off in a vacuum desiccator and the oil obtained placed in a sealed tube. Thiobenzoic acid solidifed at 24°C.

Yield, 15·5 g. (75%).



The insoluble matter obtained when the potassium salt of the acid was dissolved in water was separated. From ethyl acetate it recrystallised in small colourless plates, m.p. 132 - 133°C. This corresponds to the melting-point of dibenzoyl disulphide, $C_6H_5CO\text{-}S\text{-}S\text{-}COC_6H_5$.

On standing, the thiobenzoic acid deposited matter which was insoluble in water and alkalis. This again proved to be dibenzoyl disulphide, m.p. 131-132°C. Thus thiobenzoic acid, on standing, oxidises to dibenzoyl disulphide:-

$$2C_6H_5COSH \longrightarrow C_6H_5\text{-}CO\text{-}S\text{-}S\text{-}CO\text{-}C_6H_5.$$

Engelhardt (Zeit. fur Chemie, 1868, 354) obtained the disulphide by oxidising the potassium salt of thio-
acid
benzoic/with iodine in potassium iodide.

Several condensations carried out with thiobenzoic acid are tabulated below. The method consisted in warming about 1 g. of the acid with a slight

excess of the particular amine for one minute, pouring the mixture into water containing hydrochloric acid and filtering any solid obtained on cooling. This was washed with alkali and purified by recrystallising from alcohol. A similar reaction was carried out with benzoyl chloride in each case.

Aniline.

1 g. of the acid gave 1·1 g. (77%) of benzanilide, m.p. 161 - 162°C.

o-Toluidine.

1·9 g. of the acid gave 1·6 g. (55%) of benzo-o-toluidide, m.p. 143°C.
(Jacobson and Huber, Ber., 1908, 41, 663).

m-Toluidine.

1·3 g. of the acid gave 1·1 g. (55%) of benzo-m-toluidide, m.p. 124°C.
(Slijper, Z. Kr., 1908, 45, 407).

p-Toluidine.

1·35 g. of the acid gave 1·35 g. (65%) of benzo-p-toluidide, m.p. 159°C.
(Wallach, Ann., 1882, 214, 217).

Mesidine.

1·2 g. of benzo-mesidide (53·5%) were obtained from 1·35 g. of the acid, m.p. (plates) 205 - 206°C.
(Hübner and Sclack, Ber., 1877, 10, 1711).

Tribromaniline.

No condensation occurred with tribromaniline. The latter compound was recovered unchanged, m.p. 119°C.

p-Nitro-thiobenzoic acid.

(Hansen and Fosdick, J.A.C.S., 1933, 55, 2872).

The above authors modified Kym's method for the preparation of this acid. The modifications consist in adding the benzoyl chloride not alone, but in benzene solution. Also preliminary cooling of the alcoholic potassium hydrosulphide solution to 0°C. was carried out.

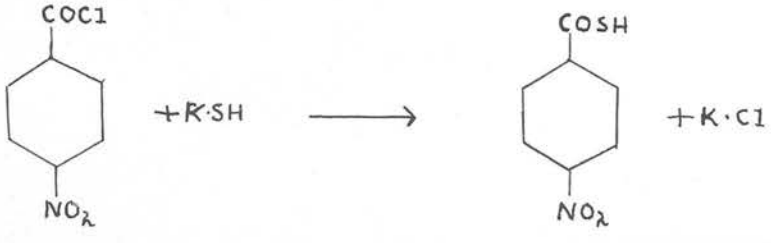
10 g. p-nitro-benzoyl chloride in dry benzene

6 g. potassium hydroxide in 120 c.c. absolute alcohol.

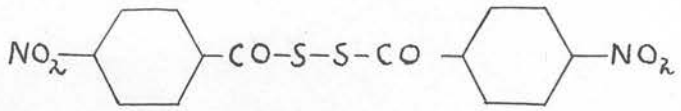
The alcoholic potassium hydroxide solution was saturated with sulphuretted hydrogen. Then the benzene solution of the nitro-benzoyl chloride was added slowly, with stirring, at 0°C. Potassium chloride was removed by filtration and the alcohol and benzene in the filtrate were drawn off in a vacuum desiccator. The potassium salt of the acid was dissolved in water and filtered from insoluble material. On adding dilute hydrochloric acid to the filtrate, the yellow thio-acid separated. It was filtered, redissolved in alkali and again precipitated with acid.

Yield, 6 g. (60%).

M.p., 96 - 98°C.



The insoluble matter obtained recrystallised in small plates from ethyl acetate, m.p. 181 - 182°C. Kym (loc. cit.) quotes 182 - 183°C. as the melting-point of bis (4-nitro-benzoyl) disulphide,



The following condensations were carried out with this acid.

Aniline.

33% of 4-nitrobenzanilide was obtained, m.p. 217 - 218°C.
(Barsilowski, Jour. Russ. Phys. Chem. Soc., 23, 73, quotes m.p. 210 - 211°C.).

o-Toluidine.

23% of 4-nitro-benzo-o-toluidide was obtained.

M.p. 157 - 159°C. A similar melting-point was obtained for the toluidide prepared from p-nitro-benzoyl chloride. The compound recrystallises from alcohol in small yellow needles.

Analysis (Micro-Dumas):

Found: N_2 10·8%.

$C_{14}H_{12}O_3N_2$ requires 10·9% N_2.

m-Toluidine.

About 25% of 4-nitro-benzo-m-toluidide, m.p. 150 - 151°C., was obtained. From alcohol the compound crystallised in small yellow needles.

Analysis (Micro-Dumas):

Found: N_2 10·9%.

$C_{14}H_{12}O_3N_2$ requires 10·9% N_2.

p-Toluidine.

4-Nitro-benzo-p-toluidide, m.p.204°C, was obtained in 25% yield. (Lellmann and Hailer, Ber., 1893, 26, 2760, give m.p. 203°C.).

Tribromaniline.

No reaction occurred with tribromaniline which was recovered unchanged.

o-Chloro-thiobenzoic Acid.

10 g. o-chloro-benzoic acid

20 c.c. thionyl chloride

9 g. potassium hydroxide in absolute alcohol.

The o-chloro benzoic acid was converted into the acid chloride by heating under reflux with thionyl chloride for one hour. Excess thionyl chloride was removed by distillation, the last traces being taken off under reduced pressure. The clear liquid obtained was dissolved in dry benzene.

Meanwhile the alcoholic-potassium hydroxide solution was saturated with sulphuretted hydrogen, giving a solution of potassium hydrosulphide.

Then the benzene solution of o-chloro-benzoyl chloride was slowly added, with rapid stirring, to the hydrosulphide solution. A yellow precipitate appeared. The mixture was heated for a few minutes on the steam-bath and the insoluble potassium chloride was filtered

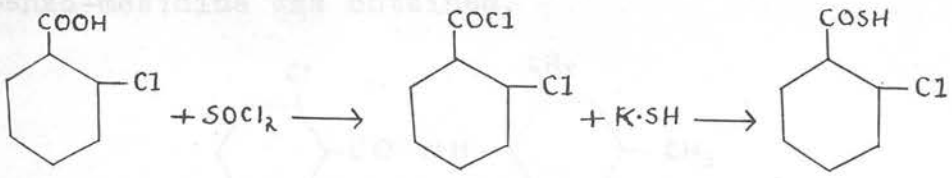
off. The alcoholic-benzene filtrate was taken to dryness in a vacuum desiccator, giving a dark yellow precipitate of the potassium salt of the thio acid. This all dissolved in water. The aqueous solution was acidified with dilute hydrochloric acid, when a heavy brown oil separated. It was extracted with ether and dried over calcium chloride. The ether was removed in a current of hydrogen, leaving a light brown oil of weight 9 g. (90%). The oil showed no tendency to solidify, even when placed in the refrigerator, but deposited a precipitate which proved to be an oxidation product.

The boiling-point of the oil was not determined, as decomposition to a black oily mass took place almost immediately on heating. Analysis and subsequent condensations proved it to be o-chloro-thiobenzoic acid, however.

Analysis (Cumming and Kay, p. 287).

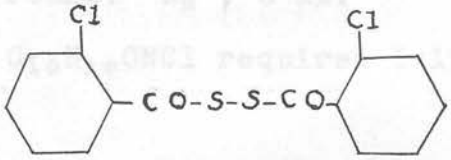
Found: sulphur, 18·6%.

C_7H_5OClS requires 18·5%



On standing, the oil deposited a solid which was insoluble in alkalis. This solid crystallised from ethyl acetate in large transparent needles, m.p. 104·5 - 105·5°C. Analysis showed this compound

to contain 18·8% sulphur and it was formulated as bis (o-chloro benzoyl) disulphide ($C_{14}H_8O_2S_2Cl_2$)



which requires 18·7% sulphur.

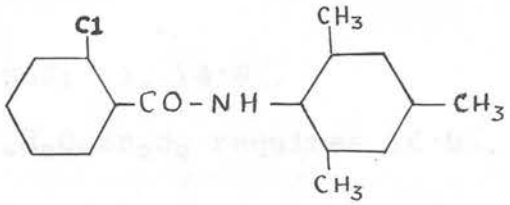
The reactions of o-chloro-thiobenzoic acid towards aniline and mesidine were examined.

Aniline.

This gave 81% of o-chloro-benzanilide, m.p. 118°C. Hübner and Wilkins (Ann., 1884, 222, 194) quote 114°C. as the melting-point of this anilide. However, the melting-point of the anilide as obtained from o-chloro-benzoyl chloride showed no change. The mixed melting-point of the two was also 118°C.

Mesidine.

With o-chloro-thiobenzoic acid mesidine liberated sulphuretted hydrogen in the cold. The reaction was completed by warming, and 61% of o-chloro-benzo-mesidide was obtained.



From alcohol it crystallised in white needles, m.p. 151 - 152°C. The melting-point of the mesidide obtained from o-chloro-benzoyl chloride was also found to be 151 - 152°C.

Analysis. (Micro-Dumas).

Found: N_2 , 5·1%.

$C_{16}H_{16}ONCl$ requires 5·1% N_2.

o-Bromo-thiobenzoic Acid.

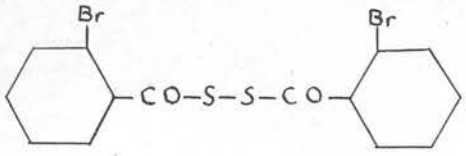
o-Bromo-thiobenzoic acid was prepared in a manner exactly similar to that employed for the preparation of the chloro-acid. Similar quantities were used and a 90% yield of the o-bromo-thiobenzoic acid was obtained in the form of a brown oil.

Analysis.

Found: S, 14·9%.

C_7H_5OBrS requires 14·7% S.

The oil, on standing, deposited a solid insoluble in alkalis. This crystallised from ethyl acetate in fine light yellow needles, m.p. 99°C. It is formulated as bis-(o-bromo-benzoyl) disulphide -



Analysis.

Found: S, 14·9%.

$C_{14}H_8O_2Br_2S_2$ requires 14·8%.

Towards aniline and mesidine o-bromo-thiobenzoic acid behaves like the o-chloro-thiobenzoic acid.

Aniline.

It gave with aniline 72% of o-bromo-benzanilide,

crystallising in colourless needles from alcohol, m.p. 123 - 124°C. This melting-point corresponds with that found by Meisenheimer (Ber., 1924, 57, 295).

Mesidine.

47% of o-bromo-benzo-mesidide was obtained. It crystallised in small white needles from alcohol and gave the m.p. 183 - 184°C.

Analysis. (Micro-Dumas).

Found: N_2 , 4·2%.

$C_{16}H_{16}OBrN$ requires 4·4% N_2.

2:4:6-Tribromo-thiobenzoic Acid.

(a) 2:4:6-Tribromo-benzonitrile.

(Sudborough, Ber., 1894, 27, 513).

10 g. tribromaniline

10 c.c. conc. hydrochloric acid in 50 c.c. water

3·5 g. sodium nitrite in 20 c.c. water

9·3 g. potassium cyanide in 30 c.c. water

10 g. copper sulphate in 30 c.c. water.

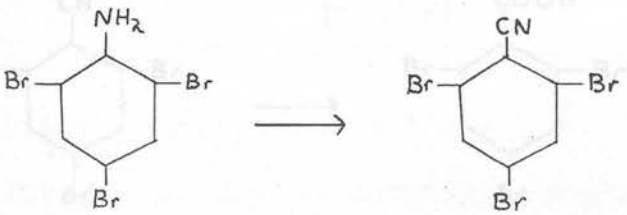
The potassium cyanide was dissolved in water by heating, and the solution of copper sulphate (also obtained by heating) was added and the mixture was heated to 90°C.

Meanwhile the tribromaniline was made into a paste with the hydrochloric acid solution to give a

fine suspension. This was well stirred and diazotised at 0°C. by the addition of the sodium nitrite solution. Any unchanged base was removed by filtration.

The diazo solution was then added, with stirring, to the potassium cyanide-copper sulphate solution maintained at 90°C. Vigorous evolution of gas occurred, and heating and stirring was continued for two hours. The mixture was cooled and the brown precipitate was filtered. It was recrystallised from alcohol.

Yield, 6 g. (53%). M.p., 127°C.



(b) 2:4:6-Tribromobenzoic acid.

(Sudborough, J.C.S., 1895, 67, 596).

6 g. 2:4:6-bribromo-benzonitrile

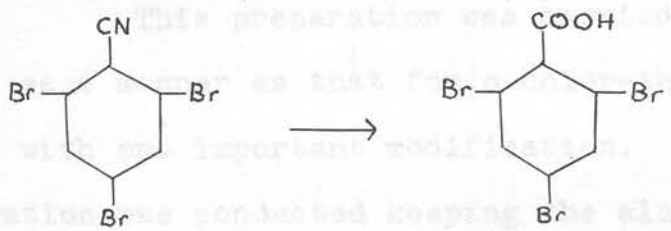
200 g. conc. sulphuric acid

3 g. sodium nitrite.

The nitrile was heated with the sulphuric acid for one hour at 130°C. This gave a clear solution of the amide. It was allowed to cool and then the sodium nitrite, dissolved in the minimum of water, was added under the surface of the liquid by means of a

tap-funnel. The solution was maintained at a temperature of 20 - 30°C. and was well stirred during the addition. The mixture was warmed on the steam-bath until all evolution of gas had ceased. It was then poured into water and the precipitate thus obtained was filtered. To remove any amide the precipitate was dissolved in sodium carbonate, and the solution filtered. Then the acid was re-precipitated with concentrated hydrochloric acid. It recrystallised from benzene in small prisms, m.p. 193 - 194°C.

Yield, 5 g. (80%).



(c) 2:4:6-Tribromo-benzoyl chloride.

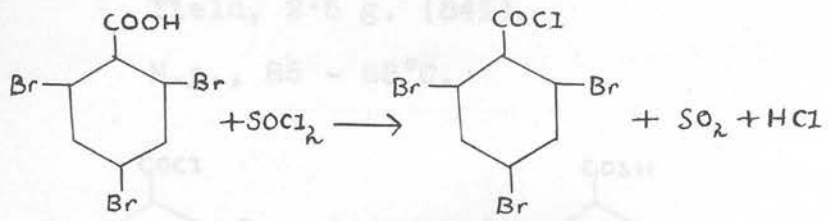
3 g. 2:4:6-tribromobenzoic acid

6 c.c. thionyl chloride.

The acid and thionyl chloride were refluxed together for two hours. Excess thionyl chloride was removed and the oil obtained solidifed in a solid cake. This was crushed up into a white powder.

Yield, 3 g. (95%).

M.p., 46 - 47°C.



(d) 2:4:6-Tribromo-thiobenzoic acid.

3 g. 2:4:6-tribromobenzoyl chloride in 10 c.c. benzene

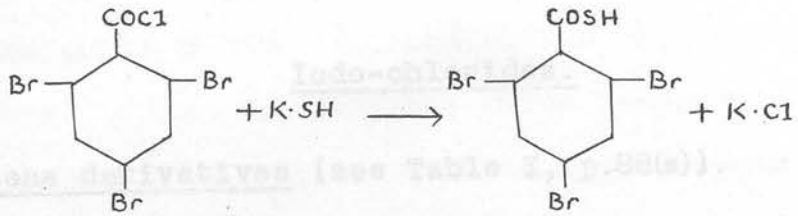
2·3 g. potassium hydroxide in 30 c.c. absolute alcohol

This preparation was carried out in almost the same manner as that for o-chlor-thiobenzoic acid but with one important modification. The whole preparation was conducted keeping the alcoholic solution at boiling-point.

The boiling alcoholic solution was saturated with sulphuretted hydrogen and the benzene solution of the acid chloride was slowly added. Heating was continued for one hour after this addition. The insoluble potassium chloride was filtered off and the alcoholic benzene filtrate was evaporated to dryness on the steam-bath. A dark brown solid was obtained, all of which dissolved in water. On acidification of this aqueous solution, a yellow precipitate separated, m.p. 82-85°C. It was redissolved in alkali and the alkaline solution was filtered. The acid was re-precipitated by acidifying the alkaline solution, filtered and dried.

Yield, 2·5 g. (84%).

M.p., 85 - 88°C.

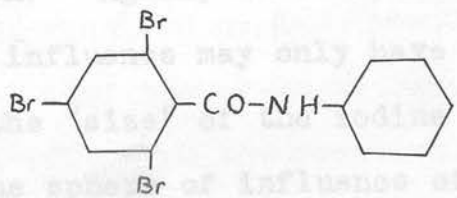


Analysis.

Found: S, 8·7%.

$C_7H_3Br_3OS$ requires 8·5% S.

With aniline this acid gave only a small yield of anilide which, after several recrystallisations from alcohol, gave m.p. of 237°C. This agrees with the melting-point of 2:4:6-tribromo-benzanilide



obtained by heating 2:4:6-tribromo-benzoyl chloride and aniline (Asinger, J. pr., 1935, 142, 296).

The acid was found to be stable and retained its property of dissolving in alkalis for several months. No oxidation product was obtained from it.

D I S C U S S I O N.

Iodo-chlorides.

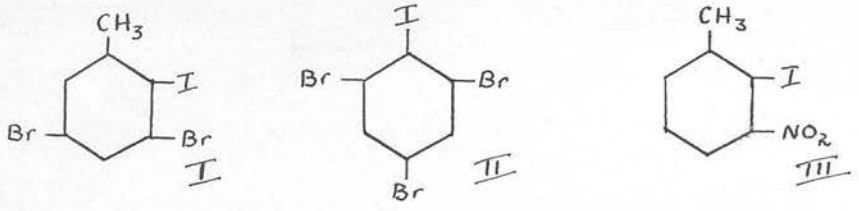
Benzene derivatives (see Table I, p.88(a)).

The main object of this work, as stated in the introduction, was an attempt to find out whether or not the formation of the aromatic iodo-chlorides is subject to the steric influences of neighbouring substituents. If the reaction follows an addition mechanism, comparable to that in the formation of the quaternary ammonium salts from tertiary amines, then steric hindrance may be expected to influence the reaction. Again, however, it was pointed out that steric influence may only have a subsidiary effect, since the "size" of the iodine atom should remove it from the sphere of influence of neighbouring substituents (see diagram, p.41(a)). How far can the above questions be answered from the results obtained?

Examination of the results obtained with the benzene derivatives shows that no general hindrance to the reaction has been encountered.

Generally the most powerful steric effects are met with in those compounds containing two ortho-situated substituents - e.g., in the esterification of acids, hydrolysis of nitriles, oxime formation of

quinones, etc. In the present case, however, although some of the diortho-substituted iodo-compounds give either a small yield of dichloride or none at all, in the majority of cases no inhibition of the reaction has occurred. For example, the three compounds, 3:5-dibromo-2-iodotoluene (I), 2:4:6-tribromo-iodobenzene (II) and 2-iodo-3-nitrotoluene (III)

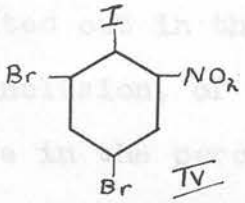


all give good yields of the corresponding dichlorides. Such groups have been proved to exert powerful hindering effects on other reactions.

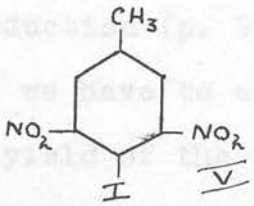
The low result obtained with iodo-mesitylene, however, requires explanation. It is not to be expected that two ortho methyl groups should exert a greater effect on the reaction than, say, two bromine atoms or one bromine atom and one methyl group. It is very probable, however, that the low result obtained in this case is due, not to the steric influences of the methyl groups, but to other factors. The extreme instability of the dichloride of iodo-mesitylene has already been indicated in the experimental section. This is probably due to the fact that nuclear chlorination of iodo-mesitylene takes place very easily, even at low temperatures. Therefore nuclear chlorination may have taken place at the expense of the other reaction, and moreover some of the dichloride may have

decomposed, giving off chlorine which may then enter the nucleus . In both cases hydrogen chloride would be evolved. A slight evolution of hydrogen chloride was actually observed. Both processes would lead to a low result, but further experiments are necessary before exact conclusions can be drawn. These experiments would endeavour to find out to what extent nuclear chlorination took place, and to what extent the dichloride was formed when a known weight of chlorine was added, say in chloroform solution.

A very low result was obtained with 4:6-dibromo-2-nitro-iodobenzene (IV), and no dichloride at all was obtained from 4-iodo-3:5-dinitrotoluene (V).



IV



V

Powerful hindrance, as indicated in other reactions, might be expected with two ortho nitro groups or with one nitro group and one bromine atom in the 2:6 positions. The result obtained with the 2:6-dibromo compound (II) is surprisingly high, however, in view of the fact that the above two diortho-substituted compounds give such low results. It might be thought that the presence of the nitro group in the ortho position was a determining factor in the appearance of the low result, but it must be pointed out against this that 2-iodo-3-nitrotoluene (III) gives an excellent yield. It is therefore difficult

to explain the low results obtained with these two compounds on a purely steric basis.

If we consider the three compounds, 2-iodo-3-nitrotoluene (III), 4:6-dibromo-2-nitro-iodobenzene (IV) and 4-iodo-3:5-dinitrotoluene (V), we find that the yield of dichloride decreases in the order stated, namely, 87·5%, 4·3% and 0%. Each compound has an ortho nitro group, the other ortho group being methyl, bromine and nitro in the order stated. Thus from these three results we can draw the conclusion that the order of effect of these three groups is:

$$CH_3 < Br < NO_2.$$

This order agrees with that found by Meyer and Kellas as pointed out in the introduction (p. 9). To draw this conclusion, of course, we have to assume that the decrease in the percentage yield of the dichloride is due, in part at least, to the presence of the second ortho-substituent. Again, however, it is not possible to state if the substituent is bringing about this decrease by a bulk effect alone since ortho-iodonitrobenzene, on the above assumption, should give a higher result than 2-iodo-3-nitrotoluene. (The former has only -H as its second ortho-substituent, whereas the latter has $-CH_3$). Instead, however, ortho-iodonitrobenzene gives a much lower result than 2-iodo-3-nitrotoluene (17·5% difference).

Therefore, although we can explain some of the gradations in results on a steric basis, it would

appear that no general conformity to steric hindrance rules is shown.

The results obtained with the mono-substituted iodo-compounds bring out the fact that the chemical nature of the substituent is not without effect on the reaction. In only one case, that of o-iodo benzoic acid, is the value practically that of the unsubstituted iodo-benzene. However, the values obtained with the iodo-nitrobenzenes show that whilst the ortho-derivative gives a much lower value than its isomers, the meta-isomer gives a higher value than the para-derivative — that is, m. > p. > o.

It was expected that the results obtained with the iodotoluenes would show a reversal of the effects found with the iodo-nitrobenzenes. In the former, the substituent groups are electron-repelling, whilst those in the latter are electron-attracting. It is true that the highest result was obtained with the ortho-iodo-toluene as contrasted with the ortho-iodo-nitrobenzene which gave the lowest value, but practically no difference was observed with the meta- and para-isomers. Further, the value obtained with p-iodotoluene is similar to that obtained with p-iodo-nitrobenzene. Consequently, it is difficult to see exactly how the reaction is influenced.

by the chemical nature of the substituent, and it is felt that further work is required before this question can be settled. One difficulty in this particular aspect of the question is the fact that the structure of the iodo-chlorides still remains to be elucidated.

There are three possibilities as to the nature of the chlorine to iodine linkages in the iodo-chlorides:-

I. Covalent linkages.

Ordinary covalent linkages require the assumption of a ring of ten electrons round the iodine atom.

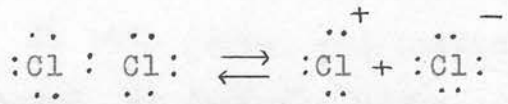
II. Singlet linkages.

The iodine octet of electrons can be retained by assuming the existence of singlet linkages comparable to those advanced for two of the chlorine atoms in phosphorus pentachloride by some people. In the latter compound, however, parachor measurements support the argument for singlet linkages, but no such support has been secured for the assumption of such linkages in iodo-chlorides. Sidgwick (J.C.S., 1931, 807) found that the dichlorides themselves were unsuitable for parachor determinations but assumed that the linkages present in the dichlorides were those still present in the salts obtained from iodoso-derivatives. He found that there was a deficiency in the observed parachor of the dipropionate derivative derived from iodoso-benzene. This deficiency, however, was much less than that to be

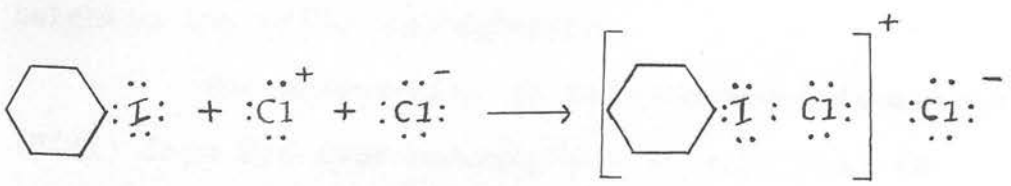
expected if singlet linkages be present. More work is necessary before this possibility can be advanced.

III. Zappi and Degiorgi (Bull. Soc. Chim., 1931, 49, 1035) suggest that the two chlorine atoms in phenyl iodo-chloride are different in nature. They base their suggestions on results obtained on acting on phenyl iodo-chloride with methyl magnesium iodide. Examination of their structure brings to light a possible mechanism for the reaction of chlorine and aromatic iodo-compounds.

As pointed out by Waters ("Physical Aspects of Organic Chemistry", 1936, p. 167), a molecule of chlorine may act as if it consisted of a pair of oppositely charged ions



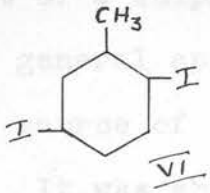
Thus one part of the molecule would be in a position to accept two electrons from the iodine atom, thereby completing its octet. The linkage between this chlorine atom and the iodine atom would be in the nature of a semi-polar bond and the remaining ion of chlorine would remain attached by an electrovalent bond.



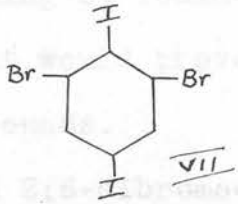
The structure of phenyl iodo-chloride given above is

that advanced by Zappi and Degiorgi, and although definite evidence for such a structure is not yet to hand, it is the most probable. It would be interesting to enquire into the orientating influence of the $-ICl_2$ group in dichlorides, as some insight into the structure might be obtained. Unfortunately, however, the iodo-chlorides are a very unsuitable class of compounds for such work.

With the two diiodo-compounds, 2:5-diiodotoluene (VI) and 1:4-diiodo-2:6-dibromobenzene (VII),



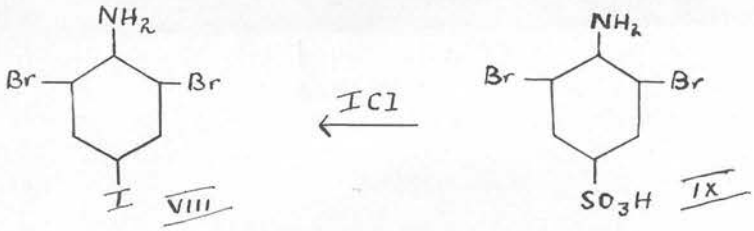
VI



VII

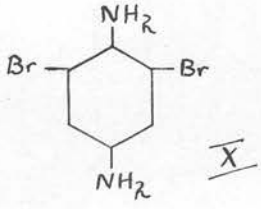
it was found that both iodine atoms reacted with chlorine. In both cases, and particularly with the former compound, no definite hindrance effects are exhibited by the iodine atom having ortho-substituents. It would be difficult to determine with the latter compound to what extent the unsubstituted iodine atom reacts more readily than that with ortho-substituents, but we can conclude that the reaction does not take place altogether at the expense of the atom which has neighbouring ortho-substituents.

The preparation of 2:6-dibromo-4-iodo-aniline (VIII) from 2:6-dibromo-sulphanilic acid (IX) is interesting.



It involves the replacement of a sulphonic grouping by an atom of iodine using iodine monochloride. As the reaction was found to proceed easily, giving a good yield of the iodo-aniline, it is thought that it might be worthy of more frequent application. If the replacement of a sulphonic grouping by iodine were found to be of general application it would prove to be a valuable source of iodine compounds.

It was shown that in 2:6-dibromo-p-phenylene-diamine (X)



the $-NH_2$ group with no ortho-substituents is diazotised in preference to the $-NH_2$ grouping neighboured by two ortho bromine atoms. This behaviour is probably due to a difference in basicity of the two amino groups and not to steric factors.

Naphthalene derivatives. (see Table II, p. 111(a)).

With one or two exceptions the naphthalene compounds studied all gave good yields of the corresponding iodo-chlorides.

α- and β-iodo-naphthalene each gave an almost theoretical yield. We can conclude, therefore, that in the α-isomer the adjoining nucleus has no effect on the reaction. It will be remembered that Pinner found that α-naphthonitrile did not give an imino-ether, whereas the β-isomer readily did so. This difference was explained on the grounds that the 8- or peri-hydrogen atom is situated closely in space to substituents in the α- or 1-position. Consequently, it may act in the same manner as an ortho-substituent in a benzene molecule and may bring about decreased reactivity in some reactions. No such decrease has been observed in this case.

It would appear that there is no clear-cut steric hindrance to be observed in the reaction with the substituted iodo-naphthalenes. The 2-nitro- and 4-nitro-α-iodo-naphthalenes give almost similar yields, showing that the presence of a nitro group in the 2-position offers no serious obstacle to the reaction. Also, no special chemical effect can be assumed to arise from the position of the nitro group. Again, with 2:4-dibromo-α-iodo-naphthalene, similar values to those found with the above two nitro compounds were obtained. Thus no gradations in yield according to the size of substituent were found. However, the low result obtained with 2-nitro-4-bromo-α-iodo-naphthalene shows that here again the reaction is not without complications.

Three substituted β-iodo-naphthalenes were

studied. Two of these, 1-bromo-β-iodo-naphthalene and 1:6-dibromo-β-iodo-naphthalene, give better yields than any of those obtained with the α-iodo-naphthalenes. It may be that in the β-compounds less hindrance is being exerted than in the α-compounds, but it is felt that the differences are not sufficient for this possibility to be seriously advanced. A low result was obtained with 1-nitro-β-iodo-naphthalene. This cannot be due to steric causes when it is remembered that less hindrance is to be expected in this case than in the isomeric 2-nitro-α-iodo-naphthalene where, indeed, a much higher yield was obtained. It may be that the $-NO_2$ group in the 1-position is able to exert an appreciable chemical influence on the iodine in the 2-position, but this question must be left open at present.

It was found that the β-iodo-chlorides were exceedingly unstable compared with the α-compounds. Whereas the latter only decomposed slowly over several months, the former all decomposed within twenty-four hours. With the dichloride of 1:6-dibromo-β-iodo-naphthalene it was shown that the decomposition was accompanied by further substitution in the naphthalene nucleus. It is thought that this line, if pursued, might lead to the isolation of interesting new chloro-naphthalenes, compounds which might not be easily obtained by other means.

In the preparation of iodo-compounds, both in the benzene and naphthalene series, Hodgson and

Walker's method of diazotisation was extensively employed. It has been found, as the above authors claim, that the method is of general application for the diazotisation of weakly basic amines. The method is capable of extension to the benzene series.

Summary.

The formation of the substituted phenyl iodo-chlorides is not subject to steric effects to the same extent as analogous reactions, such as the formation of quaternary ammonium compounds.

The low result obtained with iodo-mesitylene shows that side reactions and the instability of the dichloride must be taken into account in some cases.

The only cases observed where steric hindrance may have a serious effect on the reaction were with the compounds, 4:6-dibromo-2-nitro-iodobenzene and 4-iodo-3:5-dinitrotoluene. It is not clear, however, if this effect is purely steric.

The chemical nature of the substituents has an effect on the reaction.

No steric effects have been observed in the formation of naphthalene iodo-chlorides.

The naphthalene β-iodo-chlorides are very unstable.

Hydrolysis of Substituted Acetyl Naphthylamines.

The results obtained in the hydrolysis of the substituted α- and β-naphthalides are as expected in the light of previous work.

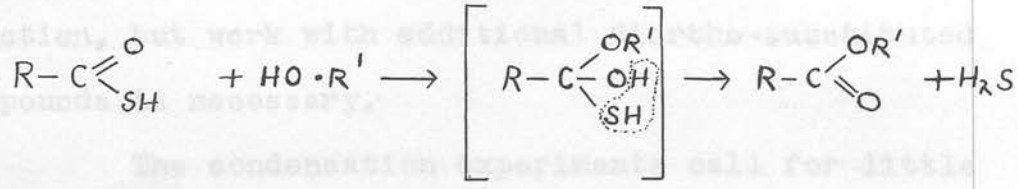
It was found that alcoholic hydrochloric acid was very efficient in effecting the hydrolysis of several α-substituted aceto-β-naphthalides. The same reagent, however, left the β-substituted aceto-α-naphthalides practically unchanged. Similar differences were found by Victor Meyer in the esterification of α-substituted-β-naphthoic acids and β-substituted-α-naphthoic acids. The former were easily esterified with alcoholic hydrochloric acid, whilst the latter resembled diortho-substituted benzoic acids in their resistance to esterification. Then again the esters of the two types of acids exhibited similar differences towards hydrolysis, the esters of α-substituted β-naphthoic acids being much more easily hydrolysed.

Consequently it may be concluded that in the hydrolysis of β-substituted aceto-α-naphthalides there is much more steric hindrance to be overcome than in the hydrolysis of α-substituted aceto-β-naphthalides. This hindrance is in part due to the adjoining nucleus, or rather to the proximity of the peri-atom of that nucleus.

Substituted Thiobenzoic Acids.

Thiobenzoic acids, as a class, have not been subjected to a thorough examination. Consequently, in applying the known methods of preparation to the isolation of new acids considerable difficulties have been encountered.

It was at first intended to study the esterification of substituted thiobenzoic acids. Reid (Am. Chem. Jour., 1910, 43, 489) showed that when alcoholic hydrochloric acid is used the most probable representation of the mechanism is:-



That is, an intermediate compound is formed which loses a molecule of hydrogen sulphide, giving the ordinary benzoic ester. This mechanism is comparable to that assumed in the esterification of carboxylic acids where steric factors are pronounced. It was thought possible that differences would be shown in the esterification of thiobenzoic acids and the corresponding carboxylic acids due to the larger "size" of the sulphur atom. As already stated, however, this line was not taken to a conclusion in the present work. Special oxygen-free apparatus would require to be used on account of the

readiness with which some of the acids are oxidised in air. As the thio-acids were studied towards the end of the research, time forbade further investigation.

Kym's original method for the preparation of thiobenzoic acid was modified by Hansen and Fosdick for the preparation of p-nitro-thiobenzoic acid. Their method was used in the present work for the preparation of o-chloro- and o-bromo-thiobenzoic acids. The fact that this method was unsuccessful for the preparation of 2:4:6-tribromo-thiobenzoic acid might signify that more energetic conditions are necessary for the isolation of diortho-substituted derivatives. It is possible that the ortho-substituents hinder the reaction, but work with additional diortho-substituted compounds is necessary.

The condensation experiments call for little comment. Perhaps the most striking feature is the fact that thiobenzoic acids do not condense with tribromaniline. This again may be due to steric effects caused by the ortho bromine atoms, and the failure of this condensation may be comparable to the failure of tribromaniline to give an anil with benzaldehyde. It would be interesting to study the condensation of thiobenzoic acids with, say, 2:4:6-tribromo-benzylamine where the $-NH_2$ group is separated from the nucleus by a $-CH_2$ group. We have not been successful as yet in synthesising this compound. Further, a comparison

between substituted thiobenzoic acids and similar thio-phenyl acetic acids will be undertaken in order to find whether any differences are exhibited by the -COSH group when it is separated from the nucleus by a $-CH_2$ group. Such a comparison would be more fundamental than Victor Meyer's comparison of substituted benzoic and phenyl acetic acids. Phenyl acetic acid is more reactive than benzoic acid, and consequently comparison of the substituted acids is complicated, but such a difference does not exist between thio-phenyl acetic acid and thiobenzoic acid.

The o-chloro and o-bromo thiobenzoic acids proved to be very active in these condensations, giving in several cases better yields of the anilides than the unsubstituted acid. That the -COSH grouping of these two ortho-substituted acids is indeed reactive is shown by the readiness with which the acids undergo oxidation in air to dibenzoyl disulphides.

One particular aspect of the thiobenzoic research which might prove of interest for further study is this oxidation to disulphides. The tribromo-thiobenzoic acid proved to be a very stable acid, and it might be possible to obtain a number of diortho-substituted acids in order to study their stability towards oxidation with iodine.

The -COSH grouping in thiobenzoic acids is apparently much more reactive than the -COOH grouping in ordinary carboxylic acids. This is shown by the

fact that the thio-acids usually react easily with amines to give anilides with the liberation of hydrogen sulphide. This reaction takes place often at once in the cold. On the other hand, carboxylic acids require prolonged heating with amines to give anilides with the loss of water. It is doubtful, however, whether this increased reactivity of the thio-acids is to be explained by the greater "size" of the sulphur atom. It is more probable that it is due to some chemical characteristic of the -COSH grouping as a whole.

SUMMARY.

An examination of the formation of the aromatic iodo-chlorides has been carried out. Difficulty was experienced in the isolation of the dichlorides of certain diortho-substituted iodo-compounds. Further, quantitative experiments have shown that this difficulty is due, in some cases, to the instability of the dichloride and to the appearance of side reactions. Therefore the quantitative results cannot be taken as being fundamental until experiments have been carried out taking all these factors into consideration. The quantitative results have shown, however, that no general hindrance to the reaction has been encountered. From scale diagrams of diortho-substituted iodobenzene molecules this is to be expected. Only in two cases - with the compounds 4:6-dibromo-2-nitro-iodobenzene and 4-iodo-3:5-dinitrotoluene — has an appreciable retardation of the reaction occurred. It is not certain whether this is due solely to steric causes.

No difference in reactivity of substituted α- and β-iodonaphthalenes has been observed.

The dichlorides of β-iodonaphthalenes have proved to be very unstable. It was shown, in the case of 1:6-dibromo-β-iodonaphthalene, that decomposition is accompanied by nuclear chlorination.

One new iodine derivative in the benzene series and two in the naphthalene series have been isolated. Several hitherto unknown dichlorides have been described.

In the course of a brief examination it has been shown that, whereas α-substituted aceto-β-naphthalides are easily hydrolysed using alcoholic hydrochloric acid, β-substituted aceto-α-naphthalides are resistant to this reagent.

Finally, condensation experiments have been carried out with certain substituted thiobenzoic acids. The method adopted for the preparation of the unknown o-chloro- and o-bromo-thiobenzoic acids is suggested as a general method for the preparation of mono-substituted thio-acids. More vigorous methods were found necessary for the preparation of the new 2:4:6-tribromo-thiobenzoic acid. In the course of this part of the research two new substituted dibenzoyl disulphides and several new substituted benzanilides were isolated. New lines for future research have been suggested.

In conclusion, the author desires to express his appreciation of the advice and assistance given him by Dr Neil Campbell during the course of this research. Grateful acknowledgment is also made to the Sir David Baxter Fund for a Scholarship.